CUR-HO 5930-30-P25745

SEPTEMBER 1991 VOL 66 No 3

Acc 12/1/92

139

VOL-66
NO. 3-4
1991

VCM

30

BRITISH HEART JOURNAL

In association with the British Cardiac Society

ditorials

193 The genetics of hypertrophic cardiomyopathy *D M Gilligan, J G F Cleland, C M Oakley*
196 Digital coronary angiography: the new gold standard? *G Hartnell, P Wilde*

riginal articles

199 Induction of a reduction in haemoglobin concentration by enalapril in stable, moderate heart failure: a double blind study *B Herrlin, O Nyquist, C Sylvén*
206 Differences in first dose response to angiotensin converting enzyme inhibition in congestive heart failure: a placebo controlled study *R J MacFadyen, K R Lees, J L Reid*
212 Cyclosporin treatment does not impair the release of nitric oxide in human coronary arteries *G S O'Neil, A H Chester, S Kushwaha, M Rose, S Tadjkarimi, M H Yacoub*
217 Genesis of Still's murmurs: a controlled Doppler echocardiographic study *H M Gardiner, H S Joffe*
221 Moderate hypothermia in the management of resistant automatic tachycardias in children *S Balaji, I Sullivan, J Deanfield, I James*
225 Atrial pacing as an adjunct to the management of post-surgical His bundle tachycardia *J A Till, E Rowland*
230 Dynamics of ventricular repolarisation in the congenital long QT syndromes *N J Linker, A J Camm, D E Ward*
238 Influence of colour Doppler echocardiography on the ultrasonic assessment of congenital heart disease: a prospective study *J P Gnanapragasam, A B Houston, W B Doig, R Fraser, S Lilley, E Murtagh, G Olafsson*

ase reports

244 Conservative surgery in multiple cusp involvement in tricuspid valve endocarditis *J R Anderson, P Scott, R U Nair* (Comment by *T Treasure*)
246 Double partitioning of the left atrium: a previously unreported echocardiographic finding in a case in which transoesophageal echocardiography aided operative resection *F A Bu'Lock, P Murphy, R P Martin*
248 Fatal rupture of an unsuspected post-traumatic aneurysm of the thoracic aorta during pregnancy *J N Townend, M K Davies, E L Jones*

British cardiology

250 British Heart Foundation surveys (1987 and 1989) of United Kingdom treatment policies for acute myocardial infarction *R Collins, D Julian*
256 **Letters to the editor**
198 **Plants in cardiology**
259 **Book reviews**
259 **British Cardiac Society newsletter**
260 **Notices**

£1

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

P, 25, 745

BRITISH
HEART
JOURNAL

In association with the British Cardiac Society
A Registered Charity

Editor: Dennis Krikler
Assistant Editors: Kim Fox, Peter Mills
Technical Editor: Jane Dawson
Editorial Assistant: Anne Oliver
Editorial Secretary: Maureen Emerson

Associate Editor: M J Davies
Statistical Adviser: Stephen J W Evans

EDITORIAL COMMITTEE

Roger M Boyle
Stuart M Cobbe
Keith Dawkins
John L Gibbs
Roger Hall
Alan B Houston
Stewart Hunter
Barry R Keeton
Michael Marmot
R Gordon Murray
John Sanderson
Tom Treasure
David E Ward
Peter Wilde
Editor: *BMJ*
Editor. *Cardiovascular Research*

NOTICE TO CONTRIBUTORS

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;296:401–5). **Authors are asked to complete a copy of the checklist provided (1991;65:59–60 (January issue)) when submitting their manuscripts for publication.** The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with wide margins.)

ETHICAL STANDARDS

Authors are expected to comply with the code of ethics known as the Declaration of Helsinki Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

CASE REPORTS should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

ABBREVIATIONS should *not* be used in the text, except for mathematical calculations and units of measurement.

REFERENCES must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

UNITS OF MEASUREMENT

All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

TABLES must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

ILLUSTRATIONS (for general requirements, please refer to *Br Heart J* 1984;51:1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible.

Echocardiograms · All unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

COPYRIGHT PERMISSION to reproduce material published elsewhere must be obtained in writing and acknowledged in the manuscript.

PROOFS of articles accepted for publication will be sent for the author's approval. Proof corrections should be kept to a minimum.

NOTICE TO SUBSCRIBERS

British Heart Journal is published monthly. The annual subscription rates are £126.00 inland and £136.00 overseas (USA $230·00). Combined rate: *British Heart Journal* and *Cardiovascular Research* £238.00 inland and £255.00 overseas (USA $443·00). Orders should be sent to The Subscription Manager, *British Heart Journal*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. (For the convenience of readers in the USA subscription orders ($230 00) with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) **All copies are despatched by air-speed.** First class rates available on request.

COPYRIGHT © 1991 by the *British Heart Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the *British Heart Journal*.

ISSN 0007–0769

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR and
printed in England by
Eyre & Spottiswoode Ltd,
London and Margate

Second class postage paid, Rahway NJ Postmaster: send address changes to British Heart Journal c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA

Br Heart J 1991;66:193–5

BRITISH
HEART
JOURNAL

Acc 12 2/93

VOL-66

Editorial

The genetics of hypertrophic cardiomyopathy

The discovery that two families with hypertrophic cardiomyopathy have mutations in the cardiac myosin heavy chain genes[1,2] may be the most important advance since the recognition of this condition in 1958.[3] It provides an opportunity to reassess our understanding of the genetics of hypertrophic cardiomyopathy and to examine the challenges posed for future study.

Clinical studies

MODE OF INHERITANCE

In an addendum to Teare's original description of eight cases of asymmetrical hypertrophy one was reported to be familial.[3] This family was subsequently investigated and found to have an autosomal dominant pattern of inheritance.[4] Several reports of single pedigrees followed and confirmed this observation.[5–8] The first large scale family screening study of hypertrophic cardiomyopathy was reported by Emanuel *et al* in 1971.[9] These investigators used clinical examination, electrocardiography, and chest *x* ray plus the results of haemodynamic investigation, operation, and necropsy, when available, to screen relatives of 76 index cases. The familial incidence was estimated to be between 30 and 50% and the data suggested that both autosomal dominant and autosomal recessive transmission occurred. We now realise that clinical examination and electrocardiography alone may be normal in up to 20% of relatives who show left ventricular hypertrophy on cross sectional echocardiography.[10] The introduction of echocardiography had a major impact on the assessment of hypertrophic cardiomyopathy and remains the cornerstone of diagnosis and therefore of family screening. Early M mode echocardiograms almost certainly over-diagnosed asymmetrical septal hypertrophy by placing the ultrasound beam off axis. Thus two M mode family studies in the early 1970s suggested that hypertrophic cardiomyopathy was familial in over 90% of cases.[11,12] Cross sectional echocardiography has increased the accuracy of wall thickness measurements. Two large family screening studies with cross sectional echocardiography were performed in the 1980s.[10,13] Both studies used the same echocardiographic criteria for the diagnosis of left ventricular hypertrophy, namely the thickness of the intraventricular septum alone or septum and posterior wall thickness > 14 mm in adults or wall thickness above the normal 95% confidence interval in children. Maron *et al* at the National Institutes of Health in the United States screened three or more first degree relatives of 70 index cases.[13] In 39 (56%) of the 70 families two or more members (including the proband) were found to be affected. In 30 (77%) of these 39 pedigrees inheritance was consistent with an autosomal dominant trait. Greaves *et al* screened 193 first degree relatives of 50 index cases in New Zealand[10] and, coincidentally, found the same familial frequency as Maron *et al*, namely 56%. In 15 (54%) of the 28 affected families transmission was autosomal dominant. In the remaining families in both studies, cases were detected in one generation only; therefore the pattern of inheritance could not be assigned. In summary, family studies to date suggest that hypertrophic cardiomyopathy is an inherited disorder in over 50% of cases. The transmission in most families is autosomal dominant. X linked inheritance has been discounted because of the many instances of father to son transmission. Autosomal recessive transmission may be the mode of transmission in some families but this remains controversial.[9,14,15]

PENETRANCE

Family studies have shown that the phenotype of hypertrophic cardiomyopathy may vary between affected members of the same family.[16] Emanuel *et al* found that isolated asymmetrical septal hypertrophy, without any other feature of hypertrophic cardiomyopathy, was compatible with a pattern of variable penetrance of an autosomal dominant gene.[17] Family studies also show that a proportion of relatives have electrocardiographic abnormalities only.[18] Such cases may represent incomplete penetrance of a hypertrophic cardiomyopathy gene. Epstein *et al* have recently identified four adults in three families who, because of their position in the pedigree, must have been obligate carriers of the gene.[19] These individuals had normal electrocardiograms and echocardiograms, although three of the four showed late potentials on signal averaged electrocardiography. It is unlikely that the presence of late potentials could reliably detect gene carriers in large studies but this report illustrates the potential for non-penetrance of a hypertrophic cardiomyopathy gene by standard echocardiographic criteria. Variable penetrance poses problems for genetic linkage studies because misclassification of individuals as unaffected leads to erroneous results. What factors influence the degree of gene penetrance in hypertrophic cardiomyopathy? Age is undoubtedly important. Previously normal teenagers can develop cardiomyopathy over several years[20] and in family screening studies higher proportions of positive cases were detected in parents than siblings and in siblings than children.[10,13] Gender may be important as males seem to be affected more often than females.[13] Factors which cause secondary hypertrophy in their own right may promote the development of hypertrophic cardiomyopathy in a genetically predisposed individual (and cause diagnostic difficulty). There is some evidence that systemic hypertension may have such an effect[21] and, although unproven, our clinical impression is that there is an excess of athletically active individuals among young people presenting with hypertrophic cardiomyopathy.[22] There are also many neurohormonal mechanisms and tissue growth factors that could be important in the development and extent of myocardial hypertrophy when a gene for hypertrophic cardiomyopathy is present. Detailed comparative studies of siblings who show different degrees of morphological disease may identify relevant factors. Serial clinical screening of the young and of equivocal cases is also necessary.

SPORADIC CASES AND CLINICAL HETEROGENEITY

All family studies report a substantial proportion, approximately 45%, of cases showing no evidence of familial transmission. These cases are termed "sporadic".[10,13] The only study that compared sporadic and familial cases found no significant differences in terms of age, sex, or echocardiographic appearances.[13] There are several potential explanations for apparently sporadic cases of hypertrophic cardiomyopathy. Other affected family members may not be identified either because they are not screened or because they have incomplete penetrance of the gene. In the New Zealand study the chance of finding an affected relative increased directly with the number of relatives screened: where six or more relatives were screened the condition was always found to be familial.[10] In some sporadic cases a new mutation may have occurred (but offspring could be affected). Sporadic cases may also be due to somatic mutations during embryonic development which affect the same genes as in the familial form but spare the germ cell line. Alternatively, sporadic cases of hypertrophic cardiomyopathy may have a polygenic or "environmental" basis or both. This becomes increasingly likely in view of the clinical heterogeneity of the condition with variants such as apical hypertrophic cardiomyopathy and "hypertrophic cardiomyopathy of the elderly" in which sporadic occurrence seems common.[22]

Genetic studies

GENETIC LINKAGE STUDIES

Genetic linkage studies produce a statistical probability known as a LOD score (logarithm of the odds) that a disease is or is not associated with a specific chromosomal location (a LOD score > 3·0 is considered evidence of positive linkage). In 1989 a group in Boston reported the first positive linkage study in hypertrophic cardiomyopathy.[23] They found strong linkage (LOD 9·4) to an area of chromosome 14 in a large French-Canadian family that had been the subject of one of the early reports.[6] Subsequently this group reported that a second family showed linkage to chromosome 14[24] and recently, investigators in Houston reported linkage to chromosome 14 in a further nine families (LOD 5·6).[25] However, there is also evidence from linkage studies that familial hypertrophic cardiomyopathy is a genetically heterogeneous disease. The Boston group reported that two families were definitely not linked to chromosome 14,[24] a report has suggested linkage to chromosome 18 in 11 Japanese families (LOD 3·1)[26] and a further report, linkage to chromosome 2 in other North American families (LOD 3·0).[27]

MUTATIONS IN CARDIAC MYOSIN HEAVY CHAIN GENES

The contractile unit or sarcomere is a regular assembly of thick filaments composed primarily of myosin heavy and light chains and thin filaments composed primarily of actin.[28] In the human myocardium there are two isoforms of myosin heavy chains—an α and a β chain.[28] The genes coding for the human α and β cardiac myosin heavy chains have been localised to chromosome 14.[29,30] The Boston group noted that the linkage site on chromosome 14 was close to these loci.[31] The group and their collaborators have proceeded to identify mutations in the myosin heavy chain genes in the affected members of both these families.[1,2] In a family of North European descent an abnormal α-β chain hybrid gene was present[1] and in the second family (the French-Canadian family of the original linkage report) a point mutation was identified.[2] This mutation would change an arginine to a glutamine residue in the functional region of the protein that binds to actin. This arginine residue is highly conserved throughout many species, suggesting that it is a site of functional importance.[2] These reports of mutations in human myosin genes shed a completely new light on the pathogenesis of hypertrophic cardiomyopathy. The preservation of systolic function in hypertrophic cardiomyopathy meant that the contractile apparatus was not a prime suspect in the search for a cause of this condition.[32]

How do these genetic defects produce hypertrophic cardiomyopathy? Two existing experimental models may help to answer this question. First, mutations in the myosin heavy chain genes of the flight muscles of *Drosophila melanogaster* result in an imbalance between the amounts of actin and myosin produced and subsequent derangement of the myofilament assembly.[33] Secondly, mutations in the *unc*-54 gene which codes for myosin heavy chain in the body wall muscle of the nematode *Caenorhabditis elegans* produce dominant phenotypes of varying severity with impaired mobility and disorganised assembly of the myofibrillar lattice.[34] These effects are due to production of an abnormal myosin heavy chain which "poisons" the assembly process.[35] Likewise, the mutations in myosin heavy chain genes found in patients with hypertrophic cardiomyopathy may produce a disruptive protein, and indeed myofilament structure is known to be disorganised in hypertrophic cardiomyopathy.[36] Detailed correlation of myocyte ultrastructure and myosin heavy chain content with genetic defects may confirm this hypothesis. Presumably, sufficient intracellular disruption of myofibrils may interfere with normal intercellular connections and thus produce myocardial disarray and hypertrophy. These genetic discoveries raise many questions about the clinical features of the disease. Why does a defect in the myosin gene in all cells often result in asymmetrical left ventricular hypertrophy? Why does hypertrophy develop typically in the teenage years? Why is there variable penetrance in individuals in the same family carrying the same mutation? The answers may lie with the control of expression of the actin and myosin gene isoforms.[28,37] For instance, the relative proportions of α and β myosin heavy chains present in human myocardium change from fetal to adult life and may vary regionally within the ventricle.[38] β myosin heavy chain is the predominant form expressed in the normal adult ventricle but the α/β ratio is affected by factors such as thyroid hormone, pressure overload, athletic training, and sex hormones.[28,37] Such factors may also influence the expression of an abnormal myosin gene and thus the morphological pattern of hypertrophic cardiomyopathy in an individual.

FAMILIES WITH NO CHROMOSOME 14 LINK

Although evidence is accumulating that a substantial proportion of familial hypertrophic cardiomyopathy is associated with genetic defects on chromosome 14, there is also clear evidence of genetic heterogeneity.[24,26,27] The proportion of cases mapped to chromosome 14 may decrease when sporadic cases and atypical forms of hypertrophic cardiomyopathy, such as apical hypertrophy cardiomyopathy and the "hypertrophic cardiomyopathy of the elderly," are studied. We already know that hypertrophic cardiomyopathy occurs as part of the clinical spectrum of many inherited conditions which have quite different genetic causes. Burn has listed 36 such disorders.[38] A large Italian family has been reported to have a fragile site on chromosome 16[39] suggesting that a gene in this region may also cause hypertrophic cardiomyopathy. Previous theories of pathogenesis based on defective regulation of cytosolic calcium and abnormal responsiveness of developing cardiac cells to sympathetic stimulation[32] are worthy of further study. Finally, the discovery that defects in myosin can produce hypertrophic cardiomyopathy will focus attention on the other proteins involved in the contractile apparatus.[28]

CLINICAL IMPLICATIONS OF GENETIC STUDIES

These rapid advances in unravelling the genetic basis of hypertrophic cardiomyopathy have implications for clinical practice in the coming years. First, different mutations in the myosin heavy chain genes may result in differences in disease severity and prognosis. Similarly, families in which the disease is not linked to chromosome 14 may differ from those in which it is, in terms of clinical disease and its treatment. Detailed documentation and presentation of the clinical features of all families studied will be necessary to identify such differences. Second, genetic analysis may become valuable when diagnosis is difficult. For instance in athletes or hypertensive patients with apparently excessive hypertrophy, genetic analysis may give a positive diagnosis of hypertrophic cardiomyopathy. Third, the ability to detect carriers of the disease gene either in utero or in childhood will now be possible in some families. This raises important ethical and practical questions about screening for and management of gene carriers. Knowledge of the natural history and pentrance of a given mutation will assist in management. To date, in both families with myosin heavy chain abnormalities all individuals with mutations in the genome had clinical disease[1, 2] but there was considerable variation in severity within the French-Canadian family[23] and studies of further families are needed. In hypertrophic cardiomyopathy there may be time to intervene before the development of morphological disease, because many individuals do not develop hypertrophy until their teenage years.[20] Elucidation of the mechanisms by which mutations in the myosin genes lead to the phenotypic abnormality combined with prospective follow up of young carriers should lead to trials of therapy to prevent hypertrophy. Finally, the discovery that mutations in the genes which code for the heavy chains of cardiac myosin may cause hypertrophic cardiomyopathy focuses attention on the role of myosin in secondary hypertrophy. The current discoveries suggest that the degree of hypertrophy for a given stimulus might reflect variations in myosin genotype.

Conclusion

The discovery that mutations in the genes that code for cardiac myosin heavy chains are the cause of hypertrophic cardiomyopathy in some families is the most important advance since the original description of the condition. Future work will identify to what extent familial hypertrophic cardiomyopathy is due to mutations in the myosin heavy chain genes and will determine how these mutations produce the condition of hypertrophic cardiomyopathy. Some families will not show defects in myosin and further studies are required to identify the genetic abnormalities in these families. Eventually we may understand how myocardial hypertrophy and disarray can be prevented.

DAVID M GILLIGAN
JOHN G F CLELAND
CELIA M OAKLEY

Department of Medicine (Clinical Cardiology),
Royal Postgraduate Medical School,
Hammersmith Hospital,
Du Cane Road,
London W12 0NN

1 Tanigawa G, Jarcho JA, Kass S, *et al.* A molecular basis for familial hypertrophic cardiomyopathy· an alpha/beta cardiac myosin heavy chain hybrid gene. *Cell* 1990;62:991–8.
2 Geisterfer-Lowrance AA, Kass S, Tanigawa G, *et al.* A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. *Cell* 1990;62.999–1006.
3 Teare D. Asymmetrical hypertrophy of the heart in young adults *Br Heart J* 1958,20·1–8.
4 Hollman A, Goodwin JF, Teare D, Renwick JW. A family with obstructive cardiomyopathy (asymmetrical hypertrophy). *Br Heart J* 1960,22:449–56.
5 Brent LB, Aburano A, Fisher DL, Moran TJ, Myers JD, Taylor WJ Familial muscular subaortic stenosis: an unrecognized form of "idiopathic heart disease", with clinical and autopsy observations. *Circulation* 1960;21:167–80.
6 Pare JAP, Fraser RG, Pirozynski WJ, Shanks JA, Stubington D Hereditary cardiovascular dysplasia: a form of familial cardiomyopathy. *Am J Med* 1961;31:37–62.
7 Horlick L, Petkovich NJ, Bolton CF. Idiopathic hypertrophic subvalvular stenosis: a study of a family involving four generations: clinical, hemodynamic and pathologic observations. *Am J Cardiol* 1966;17:411–8
8 Nasser WK, Williams JF, Mishkin ME, *et al.* Familial myocardial disease with and without obstruction to left ventricular outflow. clinical, hemodynamic and angiographic findings. *Circulation* 1967;35 638–52
9 Emanuel R, Withers R, O'Brien K. Dominant and recessive modes of inheritance in idiopathic cardiomyopathy. *Lancet* 1971;ii:1065–7.
10 Greaves SC, Roche AHG, Neutze JM, Whitlock RML, Veale AMO. Inheritance of hypertrophic cardiomyopathy· a cross sectional and M mode echocardiographic study of 50 families. *Br Heart J* 1987,58 259–66.
11 Clark CE, Henry WL Epstein SE. Familial prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis. *N Engl J Med* 1973;289:709–14
12 Van Dorp WG, Ten Cate FJ, Vletter WB, Dohmen H, Roelandt J. Familial prevalence of asymmetric septal hypertrophy *Eur J Cardiol* 1976,4: 349–57.
13 Maron BJ, Nichols PF, Pickle LW, Wesley YE, Mulvihill JJ. Patterns of inheritance in hypertrophic cardiomyopathy assessment by M-mode and two-dimensional echocardiography *Am J Cardiol* 1984;53 1087–94
14 Branzi A, Romeo G, Specchia S, *et al.* Genetic heterogeneity of hypertrophic cardiomyopathy. *Int J Cardiol* 1985,7.129–33.
15 Burn J. The genetics of hypertrophic cardiomyopathy. *Int J Cardiol* 1985;7:135–8.
16 Ciro E, Nichols PF III, Maron BJ. Heterogeneous morphologic expression of genetically transmitted hypertrophic cardiomyopathy. two dimensional echocardiographic analysis *Circulation* 1983;67:1227–33
17 Emanuel R, Marcomichelakis J, Withers R, O'Brien K. Asymmetric septal hypertrophy and hypertrophic cardiomyopathy *Br Heart J* 1983;49 309–16.
18 Autore C, Fragola PV, Picelli A, *et al.* Equivocal and borderline myocardial hypertrophy in relatives of patients with hypertrophic cardiomyopathy: possible implications in genetics of the disease. *Cardiology* 1988;75: 348–56.
19 Epstein ND, Lin HJ, Fananapazir L Genetic evidence of dissociation (generational skips) of electrical from morphologic forms of hypertrophic cardiomyopathy *Am J Cardiol* 1990;66:627–31.
20 Maron BJ, Spirito P, Wesley Y, Arce J. Development and progression of left ventricular hypertrophy in children with hypertrophic cardiomyopathy *N Engl J Med* 1986;315·610–4.
21 Karam R, Lever HM, Healy BP Hypertensive hypertrophic cardiomyopathy or hypertrophic cardiomyopathy with hypertension? A study of 78 patients. *J Am Coll Cardiol* 1989,13 580–4.
22 Gilligan DM, Cleland JG, Oakley CM The clinical and genetic heterogeneity of hypertrophic cardiomyopathy. *Current Medical Literature—Cardiovascular Medicine* 1990;9.155–61
23 Jarcho JA, McKenna W, Pare JAP, *et al.* Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14ql. *N Engl J Med* 1989;321:1372–8.
24 Solomon SD, Jarcho JA, McKenna W, *et al.* Familial hypertrophic cardiomyopathy is a genetically heterogeneous disease. *J Clin Invest* 1990;86:993–9.
25 Hejtmancik JF, Brink PA, Towbin J, *et al.* Localisation of the gene for familial hypertrophic cardiomyopathy to chromosome 14q1 in a diverse American population [abstract]. *J Am Coll Cardiol* 1991;17(suppl):165A
26 Nishi H, Kimura A, Sasaki M, *et al.* Localisation of the gene for hypertrophic cardiomyopathy to chromosome 18q [abstract] *Circulation* 1989;80 (suppl II): II–457.
27 Epstein N, Fananapazir L, Lin H, *et al.* Genetic heterogeneity in hypertrophic cardiomyopathy: evidence that HCM maps to chromosome 2p [abstract]. *Circulation* 1990,82(suppl A):III–399.
28 Nadal-Ginard B, Mahdavi V. Molecular basis of cardiac performance. *J Clin Invest* 1989;84:1693–700.
29 Saez LJ, Gianola KM, McNally EM, *et al* Human cardiac myosin heavy chain genes and their linkage in the genome. *Nucleic Acids Res* 1987,15:5443–59.
30 Matsuoka R, Yoshida MC, Kanda N, Kimura M, Ozasa H, Takao A Human cardiac myosin heavy chain gene mapped within chromosome region 14q11.2–q13 *Am J Med Genet* 1989;32.279–84.
31 Solomon SD, Geisterfer-Lowrance AA, Vosberg HP, *et al* A locus for familial hypertrophic cardiomyopathy is closely linked to the cardiac myosin heavy chain genes, CRI-L436 and CRI-L329 on chromosome 14 at q11–q12. *Am J Hum Genet* 1990;47:389–94
32 Abelmann WH, Lorell BH. The challenge of cardiomyopathy. *J Am Coll Cardiol* 1989,13:1219–39.
33 Beall CJ, Sepanski MA, Fyrberg EA. Genetic dissection of Drosophila myofibril formation: effects of actin and myosin heavy chain null genes *Genes Dev* 1989;3·131–40
34 Dibb NJ, Brown DM, Karn J, Moreman DG, Bolten SL, Waterson RH. Sequence analysis of mutations that affect the synthesis, assembly and enzymatic activity of the unc-54 myosin heavy chain gene of *Caenorhabditis elegans*. *J Mol Biol* 1985;183.543–51.
35 Bejsovec A, Anderson P. Myosin heavy-chain mutations that disrupt *Caenorhabditis elegans* thick filament assembly. *Genes Dev* 1988,2.1307–17
36 Ferrans VJ, Morrow AG, Roberts WC. Myocardial ultrastructure in idiopathic hypertrophic subaortic stenosis, a study of operatively excised left ventricular outflow tract muscle in 14 patients. *Circulation* 1972;45:769–92.
37 Lompre AM, Mercadier JJ, Schwartz K. Changes in gene expression during cardiac growth. *Int Rev Cytol* 1991;124:137–86.
38 Burn J Hypertrophic cardiomyopathy: genetics. In: Zipes DP, Rowlands DJ, eds. *Progress in cardiology*. Philadelphia: Lea and Febiger, 1990; 2/2:45–57.
39 Ferraro M, Scarton G, Ambrosini M. Cosegregation of hypertrophic cardiomyopathy and a fragile site on chromosome 16 in a large Italian family. *J Med Genet* 1990;27 363–6.

Br Heart J 1991;66:196–8

Editorial

Digital coronary angiography: the new gold standard?

Few, if any, other areas of imaging require the high spatial, temporal, and contrast resolutions that are needed for coronary arteriography. For two decades 35 mm cineangiography has fulfilled these requirements and has been regarded as the "gold standard" for the investigation of coronary artery disease; but despite its many advantages cine film has some drawbacks. Satisfactory film processing requires very careful attention to detail and is generally carried out after procedures are completed (a particular problem in some interventional procedures). Storage of film can occupy considerable space, contrast medium and radiation dosages are relatively high, and, above all, no quantitative analysis or image manipulation is possible. Digital angiography was being developed as early as 1975[1] and is now well established in non-cardiac angiography. Cine angiography, however, remained unchallenged as the imaging technique of choice for coronary artery studies right through the early development period of digital angiography whose potential for coronary imaging has only been recognised within the past few years.[2 3] Now that most major manufacturers of diagnostic *x* ray equipment are offering commercially competitive digital cardiac imaging equipment the question increasingly being asked is "Has digital imaging become the new 'gold standard' for coronary angiography?"

Overcoming limitations

Early attempts at digital coronary angiography used systems developed for peripheral angiography. Although their performance was adequate for peripheral angiography, the speed of image acquisition (up to eight frames per second), matrix size (initially 256^2), limited digital data storage (early digital discs were unable to hold even one patient's set of coronary angiograms), and the lack of adequate archiving made digital coronary angiography a cumbersome and inadequate examination. Imaging by continuous fluoroscopy with suboptimal radiographic variables produced very noisy images with much motion artefact and this severely restricted the capabilities of early systems. Technical developments occurred with increasing rapidity in the past decade and by 1985 digital cardiac imaging had progressed to a point where its potential was becoming clear.

Dedicated cardiac digital systems were found to be of particular use in the study of congenital heart disease[4–6] where the demands for spatial resolution were not quite as high as for coronary studies. It was clear that the ability to manipulate digital data had major potential advantages, not only by increasing contrast sensitivity and permitting instant subtraction techniques but also by allowing much easier quantitative analysis and other manipulation of the angiographic data. It was also clear that for paediatric imaging digital angiography allowed satisfactory anatomical imaging with worthwhile reductions in contrast and radiation dose.[7 8]

Early experience

Early studies with digital subtraction imaging of intravenous left ventriculography (IV-DSA) and low volume intra-arterial ventriculography (IA-DSA) showed that it was possible to obtain satisfactory quality ventriculograms without the arrhythmias that often degrade conventional ventriculograms. Quantification of right and left ventricular function (by either edge detection methods or videodensitometry) was easier than with cine film. Regional wall motion analysis was achieved with better spatial resolution than with radionuclide ventriculography. Digital angiography made it possible to perform exercise ventriculography by either IV-DSA or low volume IA-DSA with better spatial resolution than with radionuclide ventriculography.[9 10]

Current experience

Recent developments in digital cardiac imaging have been dramatic. Pulsed imaging using more advantageous radiographic factors has led to greatly improved signal to noise ratios, elimination of motion artefact, easier mask mode subtraction (especially with ECG advancement of the mask), and has been accompanied by improvements in image intensifier performance and optimisation of the television chain for digital rather than analogue image acquisition. Pulsed acquisition improves the signal to noise ratio by reducing the quantum mottle, which is particularly obvious with the high contrast resolution of digital systems. The intrinsic spatial resolution of a new caesium iodide image intensifier is typically 4–5 line pairs/mm but this can deteriorate to as low as 2 line pairs/mm over time. This compares with a resolution of about 2 line pairs/mm for a 512^2 matrix on a 17 cm image intensifier. Although this spatial resolution may be inferior to that of cine film, the greater contrast sensitivity compensates for the poorer spatial resolution so that the overall perceived resolution, which contains the diagnostic information, is similar or better than for conventional cine studies. Commercially available cardiac digital systems commonly offer acquisition on a 512^2 matrix at 25 frames per second. 1024^2 matrices are now available, although with lower frame rates. Although the denser matrix has a resolution approaching that of the best image intensifiers it is not clear whether this produces more diagnostic information. The use of a 1024^2 matrix does require the use of a higher radiation dose to reduce the effect of quantum mottle and produces four times more data for storage than a 512^2 matrix, typically limiting image acquisition to 6 frames per second. Biplane studies can be recorded on digital imaging but if the computer shares its function between two planes, the frame rate of each will be halved. It has now been shown in several studies that digital coronary imaging compares very favourably with cine imaging in fulfilling the exacting demands of coronary arteriography.[11 12]

Improvements in computer design allow the acquisition and processing of huge quantities of data. Less than 10 years ago the best systems could only acquire data at 8 frames per second (512^2 matrix) with a maximum of 300 images being stored on the hard disc (37 seconds or about half of one complete examination). Image analysis and selection for archiving (to analogue video tape or sheet film) had to be done during the examination and had to be completed before the next patient could be examined. Simultaneous image acquisition and analysis was not possible. By using multiple hard discs, data compression techniques, fast processors, and task sharing a whole day's work can now be stored on the computer and can be analysed without disrupting subsequent examinations. Currently available equipment can store up to 26 000 images. If single plane acquisition is on a 512^2 matrix at 25 frames per second this allows the storage of about 17 minutes of filming (equivalent to 13 patients examined in 10 projections and imaged for an average of eight seconds in each projection).

Advantages

The obvious immediate advantage of high quality digital imaging is the availability of instant final quality images. This has particular advantages in monitoring the progress of coronary angioplasty or other interventional procedures[13] and various image storage and "road mapping" techniques have been used. Once the digital image has been acquired the data can be processed in various ways. Experience with current systems suggests that subtraction techniques add little to the usefulness of a digital coronary study. Changing contrast levels, windowing, and defining edges can improve the quality of the image and to some extent will compensate for any radiographic shortcomings. Automatic techniques for stenosis measurement or flow estimation can use edge defining techniques[14 15] or densitometry.[16-18] Functional data related to regional blood flow can be derived by various analytical techniques. The precision with which digital data are presented should not obscure the fact that the technique has some inherent potential for inaccuracy,[12] for example, flare, beam-hardening, and scatter may contribute to measurement errors which can in turn lead to errors in stenosis estimation.

Archiving and review of cine angiocardiograms has always been a significant problem with cine films requiring large amounts of storage space and dedicated projectors for viewing. Digital imaging is not without its storage and display problems also. Early digital images could only be archived as processed images on sheet film or on analogue videotape because of restrictions on the amount of digital data that could be stored on conventional floppy or hard discs. Much of the data acquired at great expense by using digital angiography was therefore lost. Archiving on analogue video cassette allows easy access to the images, provided that a separate cassette is used for each patient and high quality video display equipment is available; but downloading on to analogue videotape prohibits further digital image manipulation.

The development of digital video cassettes means that a complete digital examination can be archived and recalled at a later date for reanalysis. This can be an expensive and bulky option—though it still requires less storage space than cine film. Replay has to be through the digital processor to which access may be limited because the system may well be in use for examining another patient. Alternatively, the fully processed digital images can be recorded on to high resolution mini-video cassettes, which have a much better performance than conventional video cassettes, take up little storage room, and can be replayed through conventional video recorders. Quantitative data on ventricular function and stenosis estimation can be recorded on a video cassette or hard copy imager such as a laser imager. At present there is still no generally available, cheap, and convenient method of recording and displaying the digital data for routine clinical viewing, but newer forms of data storage will become available to overcome these problems. The decisions in selecting a new digital system will be many, but one of the most important will be the mode of image storage and the display that best suits the working patterns of individual departments.

Radiation dosage for both patient and staff can be reduced by the use of digital imaging but such reductions may not be substantial if image quality is to be maintained. High quality images still require high doses of radiation to produce sufficient image detail (reduce quantum mottle) and it is not primarily in the radiation dose per frame that reductions are easiest to achieve, though some reduction is possible. Important radiation dose reduction in coronary arteriography has been shown in some systems by the use of "gap-filling" techniques in which the *x* ray pulse rate can be halved (for example from 25 to 12 ½ frames per second) but each frame is digitally duplicated. This eliminates flicker but still allows high quality diagnostic images to be presented smoothly to the viewer. This technique halves radiation doses. In an analogous fashion, digital pulsed fluoroscopy systems can also reduce radiation doses. The capital cost of a new digital system is a little greater than for a conventional system but the difference is getting smaller. There are savings to be made with digital systems, particularly in running costs. Expensive cine film and processing equipment is eliminated as well as the staff time taken to do this. Contrast medium volumes or concentrations can be reduced too. Finally the speed of procedures can be increased because instant high quality images are available for review; this is particularly relevant to interventional work.

Conclusion

For a long time there has been doubt about whether the practical problems of digital angiocardiography, particularly those related to resolution and to image storage and review, have been overcome sufficiently to make it worth taking the major step from a cine to a digital department. With the currently available digital equipment which can acquire images of equal or better quality than cine film and store them with increasing ease, it seems that the case for going digital is now overwhelming and this will soon be the "gold standard" technique for coronary arteriography.[19 20]

GEORGE HARTNELL

Department of Clinical Radiology,
New England Deaconess Hospital,
Boston, Massachusetts 02215,
USA

PETER WILDE

Department of Radiodiagnosis,
Bristol Royal Infirmary,
Bristol BS2 8HW

1 Heintzen PH, Brennecke R, Bursch JH. Automated videoangiographic image analysis. *Computers in cardiology*. Long Beach: IEEE Computer Society, 1975:55–64.
2 Mancini GBJ, Higgins CB. Digital subtraction angiography; a review of cardiac applications. *Prog Cardiovasc Dis* 1985;**18**:111–41.
3 Neeley JP III, Vannier MW, Gutierrez FR, Spadaro JJ Jr. Digital subtraction angiography of the coronary arteries. *Crit Rev Diagn Imaging* 1985;**25**:23–60.
4 Buonocore E, Pavlicek W, Modic MT, Meaney TF, O'Donovan PB, Grossman LB, *et al*. Anatomic and functional imaging of congenital heart disease with digital subtraction angiography. *Radiology* 1983;**147**:647–54.
5 Dickinson DF, Wilson N, Partridge JB. Digital subtraction angiography in infants and children with congenital heart disease. *Br Heart J* 1984;**51**:485–91.
6 Tonkin ILD, Fitch SJ, Magill HL, Gerald BE, Gold RE, Alpert BS, *et al*. Pediatric digital subtraction angiography: intra-arterial and intracardiac

applications. *Pediatr Radiol* 1986;**16**:126–30.

7 Levin AR, Goldberg HL, Borer JS, Rothenberg LN, Nolan FA, Engle MA, *et al*. Digital angiography in the paediatric patient with congenital heart disease; comparison with standard methods. *Circulation* 1983;**68**:374–84.

8 Bogren HG, Bursch JH. Digital angiography in the diagnosis of congenital heart disease. *Cardiovasc Intervent Radiol* 1984;7:180–8.

9 Bellamy GR, Yiannikas J, Detrano R, Simpfendorfer C, Salcedo EE. Detection of multivessel disease after myocardial infarction using intravenous stress digital subtraction angiography. *Radiology* 1986; **161**:685–9.

10 Detrano R, Yiannikas J, Simpfendorfer C, Hobbs RE, Salcedo EE. Exercise digital subtraction ventriculography for the detection of ischaemic wall motion abnormalities in patients without myocardial infarction. *Br Heart J* 1986;**56**:131–7.

11 Goldberg HL, Moses JW, Fisher J, Tamari I, Borer JS. Diagnostic accuracy of coronary angiography utilizing computer-based digital subtraction methods: comparison to conventional cineangiography. *Chest* 1986;**90**: 793–7.

12 Gurley JC, Nissen SE, Booth DC, Harrison M, Grayburn P, Elion J, *et al*. Comparison of simultaneously performed digital and film-based angiography in assessment of coronary artery disease. *Circulation* 1988;**78**: 1411–20.

13 Katritsis D, Lythall DA, Anderson MH, Cooper IC, Webb-Peploe MM. Assessment of coronary angioplasty by an automated digital angiographic method. *Am Heart J* 1988;**116**:1181–7.

14 Ratib OM, Mankovich NJ. Quantitative coronary arteriography: design and validation. *Radiology* 1988;**167**:743–7.

15 Popma JJ, Eichhorn EJ, Dehmer GJ. In vivo assessment of a digital angiographic method to measure absolute coronary artery diameter. *Am J Cardiol* 1939;**64**:131–8.

16 Ikeda H, Koga Y, Utsu F, Toshima H. Quantitative evaluation of regional myocardial blood flow by videodensitometric analysis of digital subtraction coronary arteriography in humans. *J Am Coll Cardiol* 1986;**8**:809–16.

17 Lefree MT, Simon SB, Mancini J, Bates ER, Vogel RA. A comparison of 35 mm cine film and digital radiographic image recording: implications for quantitative coronary arteriography. *Invest Radiol* 1988;**23**:176–83.

18 Simons MA, Muskett AD, Kruger RA, Klausner SC, Burton NA, Nelson JA. Quantitative digital subtraction coronary angiography using videodensitometry: an in vivo analysis. *Invest Radiol* 1988;**23**:98–106.

19 Pepine CJ. The cardiac catheterization laboratory—1990. *Am J Cardiol* 1990;**66**:37F–40F.

20 Tobis J, Henry W, Nalcioglu O. Cardiac digital angiography. In: Brundage BH, ed. *Comparative cardiac imaging*. Rockville: Aspen, 1990:47–63.

PLANTS IN CARDIOLOGY

Royal Botanic Gardens, Kew.

Papaver somniferum L.
Stephenson J, Churchill J M. *Medical botany*. London: 1836, volume 3, plate 159.

Verapamil and morphine

When the unripe seed capsule of the opium poppy *Papaver somniferum* (Papaveraceae) is incised a milky fluid exudes. The dried juice, opium (from the Greek, opos, juice), has been used medicinally for over 5000 years. The 25 or so alkaloids of opium belong to two distinct chemical classes with quite different actions. Morphine and codeine belong to the phenanthrene class. Papaverine, which accounts for only 1% of the alkaloids, is in the benzylisoquinoline class and was isolated in 1848. But its lack of analgesic activity inhibited pharmacological investigation until 1917 when David Macht initiated this at Johns Hopkins Medical School. Because it relaxes smooth muscle it is a good vasodilator; in cardiac muscle it depresses conduction and prevents chloroform induced ventricular fibrillation. But Paul D White found it to be of little use in angina or hypertension and it was tried without success in cardiac arrhythmias. Nevertheless, papaverine and its synthetic analogues were popular as antispasmodic drugs for gastrointestinal and genitourinary ailments and in 1937 the German pharmaceutical firm Knoll asked their chemist, Ferdinand Dengel, to synthesise it. He worked on the compound for over 20 years and in May 1959 he produced an analogue, D365 (D for Dengel), which was soon shown to be pharmacologically much more active than other analogues or other similar drugs. Unlike other vasodilators it had negative inotropic and chronotropic effects. It was iproveratril, later to be called verapamil, and was marketed as Isoptin. Because it was thought to be a β blocker clinical trials in angina began in 1961. Fleckenstein's study of verapamil started in 1963 and led to his seminal discovery of calcium antagonism as its mode of action. In 1972 Schamroth, Krikler, and Garrett (*British Medical Journal* 1972;**i**:660–2) were the first to link the clinical action of verapamil in terminating arrhythmias with Fleckenstein's concept of calcium channel blockade.

Morphine, still pre-eminent for pain relief, was formerly valuable in acute left ventricular failure, and in 1942 Crighton Bramwell and J T King said, "morphine acts as a specific and what is more it is the only drug which is effective."

Papaver somniferum originated in the western Mediterranean and is cultivated chiefly in Asia and Tasmania. Its seed is free of opium and is used on bread. The poppy family, Papaveraceae, has 23 genera and 210 species, mostly in the northern hemisphere. None of its other species has alkaloids that are either better or different from those in the opium poppy.

A HOLLMAN

ORIGINAL ARTICLES

Induction of a reduction in haemoglobin concentration by enalapril in stable, moderate heart failure: a double blind study

Bo Herrlin, Olof Nyquist, Christer Sylvén

Abstract

Objective—**To study the long term effects (12 weeks) of enalapril on central haemodynamic function and on arterial oxygen content and its determinants—haemoglobin concentration and oxygen saturation—in patients with stable moderate heart failure.**

Design—**Double blind placebo controlled randomised study.**

Patients—**17 patients with stable moderate heart failure caused by dilated cardiomyopathy which was treated with diuretics and digoxin.**

Methods—**Central haemodynamic function, arterial oxygen content, arterial haemoglobin concentration, and arterial oxygen saturation were measured at rest and during submaximal exercise. Plasma volume and total body haemoglobin were determined at rest.**

Results—**With enalapril treatment heart rate, pulmonary capillary wedge pressure, mean arterial pressure, and systemic vascular resistance decreased significantly both at rest and during submaximal exercise. Cardiac output did not change at rest but tended to increase (p = 0·06) during submaximal exercise. Arterial oxygen saturation remained unchanged while haemoglobin concentration and arterial oxygen content were significantly reduced. Total body haemoglobin was significantly reduced but the plasma volume remained unchanged. At rest, the reduction in arterial oxygen content resulted in a significantly reduced mixed venous oxygen content. However, during submaximal exercise the increase in cardiac output fully compensated for the reduction in arterial oxygen content and this effect was indicated by the unaltered mixed venous oxygen content. No changes were found in the placebo group after twelve weeks.**

Conclusions—**Enalapril unloads the heart and reduces haemoglobin concentration. During submaximal exercise, the improvement in systemic blood flow was counterbalanced by this negative effect on the oxygen carrying capacity and systemic oxygen delivery was unchanged.**

Cardiac Division, Department of Medicine, Huddinge University Hospital, Stockholm, Sweden
B Herrlin
O Nyquist
C Sylvén

Correspondence to
Dr Bo Herrlin,
Department of Medicine,
Huddinge University
Hospital, S-141 86
Huddinge, Sweden.

Accepted for publication
12 March 1991

In heart failure the capacity of cardiac output to increase during exercise is impaired and this reduces the systemic delivery of oxygen. Long term treatment with angiotensin converting enzyme inhibitors can improve cardiac output both at rest and during exercise[1-3] but the effects of the treatment on arterial oxygen content are not known.

Erythropoietin, an important regulator of erythropoiesis, is mainly produced in the kidney.[4] There is evidence that the renin-angiotensin system modulates, directly or indirectly, the release of this hormone.[5-7] Studies have also shown that angiotensin converting enzyme inhibition exacerbates anaemia in chronic haemodialysis patients with hypertension[8] and lowers the haematocrit in hypertension.[9]

The purpose of this double blind placebo controlled randomised study was to determine whether long term angiotensin converting enzyme inhibition with enalapril has any influence on the haemoglobin concentration and to evaluate the effect on systemic oxygen delivery both at rest and during submaximal exercise in a homogeneous group of patients with stable moderate heart failure caused by dilated cardiomyopathy.

Patients and methods

PATIENTS

We studied 19 patients (16 men and three women (41–62 years old (mean (SD)) 51 (6) years)) with moderate heart failure caused by dilated cardiomyopathy, which was treated with digoxin and frusemide. None of the patients had oedema and all had been clinically stable for at least two weeks. Inclusion criteria were an echocardiographically determined left ventricular end diastolic diameter of > 60 and > 30 mm/m^2, a left ventricular shortening fraction of < 20%, and an exercise capacity of > stage III and < IX, according to a revised Naughton protocol.[10] We excluded patients with primary valve disease, suspected ischaemic heart disease or congenital valve disease, those taking concomitant vasodilating agents, and those with right sided heart failure caused by pulmonary disease. The study protocol was approved by the local ethics committee. All patients gave their informed consent before entering the study.

PROTOCOL

The patient was admitted to hospital. The daily doses of digoxin and frusemide remained unchanged during the baseline study period before randomisation. On the first day the blood volume, venous haematocrit, venous haemoglobin concentration, serum potassium, and serum sodium were determined and echocardiography, a chest *x* ray, and a symptom limited exercise test were performed. The total blood volume was measured by the ^{131}I-labelled serum albumin method. The haematocrit and haemoglobin concentration were determined in venous blood from an antecubital vein. Echocardiography was performed on patients in the left lateral position (ATL Mark III, 13 mm and 3 MHz transducer). Left ventricular end diastolic and end systolic diameters were measured.[11] The mean value of five consecutive beats was calculated. The left ventricular shortening fraction was derived from the difference between left ventricular end diastolic and end systolic diameters divided by left ventricular end diastolic diameter. Cardiac volume was measured radiologically by Jonsell's method.[12] Patients performed the exercise test sitting on an electrically braked ergometer. The load was increased every two minutes according to a modified Naughton protocol[10]:

	Stage								
	I	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*IX*
W	10	20	30	50	70	90	110	130	150

The patients exercised until limiting symptoms developed—that is dyspnoea or fatigue or both. Perceived exertion was rated on the scale designed by Borg.[13]

On the second day the patient was made familiar with the catheterisation laboratory and with the ergometer on the catheterisation table. Patients chose the highest load that they believed they could maintain for 10 minutes in the supine position. This was used as the submaximal load during the cardiac catheterisation. On the second day renal plasma flow was determined by *p*-aminohippurate and creatinine clearance was calculated from 24 hour urine collections and serum creatinine. The reference values in healthy subjects were 500–800 ml/min and 85–145 ml/min respectively.

On the third day, at 5.30 am, the patient was given a light breakfast and his or her daily dose of digoxin and frusemide. The right ventricle was catheterised at 8 am. A triple lumen balloon tipped thermodilution catheter (Edwards Laboratory, USA) was introduced via an antecubital or femoral vein under fluoroscopic guidance and was used to measure right atrial, pulmonary arterial, and pulmonary capillary wedge pressures. A polyethylene arterial catheter was introduced into the brachial or femoral artery to measure the systemic pressure. The measurements of haemodynamic function were made with the zero reference level at the mid-axillary line. Cardiac output was measured by a cardiac output computer (Cardiac Computer, Edwards Laboratories, model 9520) with the use of an iced injectate. Heart rate was derived from a continuously recorded electrocardiogram. Blood was taken from the pulmonary artery lumen of the Swan-Ganz catheter for mixed venous samples and from the arterial catheter for arterial samples.

After about 30 minutes of rest haemodynamic recordings were performed and samples of arterial blood were taken to measure blood gases, blood lactate, and plasma noradrenaline. Samples of arterial blood and mixed venous blood were taken simultaneously for analyses of oxygen saturation and haemoglobin concentration. After three minutes of exercise pressures were determined according to the protocol and cardiac output was measured. After approximately six minutes of exercise blood samples were taken for the same determinations as before exercise.

After the exercise test the patient was randomised to placebo or 10 mg enalapril twice a day by mouth. Then frequent samples were taken for 24 hours for blood measurements; this caused a significant decrease in haemoglobin concentration.

The patient was seen every two weeks for eight weeks. Haemoglobin concentration was determined in venous blood drawn from an antecubital vein. After 12 weeks the patient was admitted to hospital for a repeat study with the same workload as in the submaximal exercise test at baseline.

BLOOD ANALYSES

Blood lactate was analysed by a semiautomatic system based on flow injection analysis with a coefficient of variation of 4·9%.[14] Blood oxygen saturation and haemoglobin concentration were determined photometrically with an Osmo 2-Hemoximeter (Radiometer, Copenhagen). Plasma noradrenaline was measured by liquid chromatography with electrochemical detection.[15] The upper reference limit in normal subjects at rest was 2·3 nmol/l.

ANALYSES

Mean right atrial pressure (RAP), mean pulmonary capillary wedge pressure (PCWP), and mean systemic arterial pressure (MAP) were determined by electronic integration. Cardiac output (CO) was determined in triplicate. Heart rate (HR) was determined for one minute. Derived variables were calculated as follows:

Systemic vascular resistance = 80 × (MAP − RAP)/CO (dyn.s.cm^{-5}).

Blood oxygen content = per cent oxygen saturation × haemoglobin concentration × 1·34 ml oxygen/haemoglobin (ml/l).

Arteriovenous oxygen difference (AVo_2) = arterial oxygen content − mixed venous oxygen content (ml/l).

Systemic oxygen delivery = CO × arterial oxygen content (ml/min).

Oxygen uptake (Vo_2) = AVo_2 × CO/body weight (ml/min/kg).

Plasma volume = blood volume (1 − 0·88 × venous haematocrit) (l).[16]

Total body haemoglobin = blood volume × venous haemoglobin concentration × 0·91 (g).[17]

Table 1 Clinical characteristics and non-invasive findings of patient groups at baseline

Characteristic	*Placebo (n = 9)*	*Enalapril (n = 8)*
Age (yr)	53 (4)	47 (6)
Sex (F/M)	1/9	2/8
Duration of symptoms (mnth):		
Mean (SD)	21 (12)	38 (28)
Median (range)	17 (6–36)	25 (3–89)
Symptom-limited exercise test exercise duration (s)	701 (93)	753 (150)
Echocardiography		
LVEDD (mm)	71 (8)	78 (11)
FS (%)	11 (4)	11 (3)
Chest x ray heart volume (ml/m^2)	712 (144)	826 (157)

Difference between groups were all non-significant
FS, left ventricular fractional shortening; LVEDD, left ventricular end diastolic diameter.

STATISTICAL ANALYSIS

Values are given as means (SD). Changes within groups were tested by paired *t* tests. Unpaired *t* tests were used to evaluate differences between two groups. Multiple comparisons of repeated measurements were tested by analysis of variance and Fisher's test for a protected least square significant difference. A p value $< 0{\cdot}05$ was regarded as significant.

Results

Table 1 shows the clinical characteristics and non-invasive findings. Nine patients were randomised to placebo and ten to enalapril 10 mg twice a day. One patient on enalapril died suddenly after six weeks. During the study another patient on enalapril showed changes in haemoglobin concentration that were different from the remaining 17 patients. He showed the greatest absolute and relative changes in blood volume after 12 weeks compared with baseline (>2 SD compared with the remaining patients) and the greatest absolute and relative changes in haemoglobin concentration after 12 weeks compared with baseline, six weeks, and eight weeks (>2 SD, >2 SD, and >3 SD respectively) compared with the 17 remaining patients. Values for this patient were therefore regarded as outliers reflecting unstable vascular homoeostasis. These two patients were excluded from further analysis. All patients completed the protocol without complications.

The frusemide dose was increased in two patients in the placebo group because of increased dyspnoea. During the first week the daily dose of frusemide was reduced in three patients in the enalapril group because of symptomatic hypotension and this reduced dose was maintained throughout the study period. None of the patients had peripheral oedema during the study and all had normal plasma sodium concentrations.

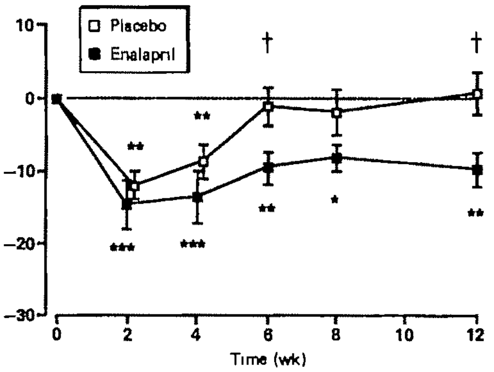


Figure 1 Absolute changes (mean (SEM)) in haemoglobin concentration in venous blood over 12 weeks. Differences within groups compared with baseline are indicated as $*p < 0{\cdot}05$, $**p < 0{\cdot}01$, $***p < 0{\cdot}001$. *Differences in changes from baseline between groups are indicated as* $\dagger p < 0{\cdot}05$.

Body weight, blood volume, and plasma volume did not change in the two groups. Total body haemoglobin was reduced in the enalapril group but remained unchanged in the placebo group (table 2).

Creatinine clearance increased and renal plasma flow tended to increase (+30 (59)%, $p < 0{\cdot}10$) with enalapril. Creatinine clearance increased considerably by 32 (18) ml/min in the three patients in whom the dose of diuretics was reduced whereas in the remaining five patients it increased by 6 (11) ml/min. No changes were found in the placebo group. Serum creatinine (table 2), serum potassium, and serum sodium did not change in either group.

Exercise duration and perceived exertion during the symptom limited maximal exercise test remained unchanged in both groups (table 2).

VENOUS HAEMOGLOBIN CONCENTRATION DURING THE 12 WEEK STUDY

After two weeks, compared with baseline, the haemoglobin concentration was reduced in both groups (fig 1). With placebo at six weeks the haemoglobin concentration was restored to the baseline value and then remained unchanged. With enalapril the haemoglobin concentration was incompletely restored at six weeks and remained at a value significantly below baseline for the rest of the study period.

Table 2 Weight, blood volume, total body haemoglobin, renal function, and exercise capacity (mean (SD))

	Baseline		*12 weeks*	
Data	*Placebo (n = 9)*	*Enalapril (n = 8)*	*Placebo (n = 9)*	*Enalapril (n = 8)*
Weight (kg)	79 (14)	84 (11)	80 (15)	82 (10)
Blood volume (l)	5·8 (1·4)	6·2 (1·0)	5·6 (1·3)	6·0 (0·8)
Plasma volume (l)	3·5 (0·7)	3·8 (0·6)	3·3 (0·6)	3·8 (0·5)
Total body haemoglobin (g)	779 (240)	880 (188)	756 (225)	782 (135)*
Creatinine clearance (ml/min)	96 (28)	89 (16)	101 (37)	105 (17)*
Renal plasma flow (ml/min)	390 (130)	349 (92)	427 (83)	416 (99)
Serum creatinine (μmol/l)	96 (17)	100 (17)	91 (15)	97 (17)
Exercise duration (s)	701 (93)	753 (150)	650 (145)	753 (164)
Perceived exertion (Borg[13])	16 (1)	16 (1)	17 (1)	16 (1)

Differences compared with baseline within groups, $*p < 0{\cdot}05$.

Table 3 Haemodynamic, metabolic, and hormonal measurements (mean (SD))

	Rest			
	Placebo (n = 9)		*Enalapril (n = 8)*	
	Baseline	*12 weeks*	*Baseline*	*12 weeks*
HR (beats/min)	83 (14)	86 (15)	91 (25)	79 (16)***†
PCWP (mm Hg)	13 (7)	11 (9)	20 (12)	12 (6)*
MAP (mm Hg)	87 (11)	85 (13)	92 (12)	75 (8)**†
CO (l/min)	4·7 (0·8)	4·6 (0·7)	4·4 (0·8)	4·5 (1·1)
SVR (dyn.s.cm^{-5})	1462 (342)	1470 (404)	1609 (305)	1311 (315)*†
Arterial Hb (g/l)	147 (15)	147 (18)	155 (11)	142 (12)**‡
Arterial O_2 sat (%)	96 (1)	96 (2)	97 (1)	98 (1)
Arterial O_2 (ml/l)	192 (20)	190 (24)	204 (14)	188 (14)*†
PaO_2 (kPa)	10·9 (1·3)	10·6 (1·4)	11·0 (0·7)	12·0 (1·1)
$\dot{V}O_2$ (ml/kg/min)	3·7 (0·8)	3·5 (0·6)	4·0 (0·6)	3·6 (0·4)
Arterial lactate (mmol/l)	0·8 (0·2)	0·9 (0·2)	0·8 (0·3)	0·9 (0·3)
PNA (nmol/l)	2·7 (0·8)	2·6 (0·8)	3·1 (1·4)	2·2 (0·9)**†

Differences compared with baseline within groups. *p < 0·05, **p < 0·01, ***p < 0·001.
Differences in change from baseline between groups: †p < 0·05, ‡p < 0·01, ††p < 0·001.
CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; PNA, arterial plasma noradrenaline, SVR, systemic vascular resistance; VO_2 = oxygen uptake.

Haemoglobin concentration decreased by 7, 7, and 10 g/l respectively in the three patients in whom the dose of diuretics was reduced, while in the remaining five patients it fell by 18 (9) g/l.

HAEMODYNAMIC FUNCTION

In the enalapril group—both at rest and during submaximal exercise—heart rate, pulmonary capillary wedge pressure, mean arterial pressure, and systemic vascular resistance were reduced (table 3). During submaximal exercise cardiac output tended to increase (p = 0·06). No changes were noted in the placebo group.

OXYGEN TRANSPORT

In the enalapril group haemoglobin concentration and arterial oxygen content were reduced while both arterial oxygen pressure and arterial oxygen saturation were unchanged (table 3). Systemic oxygen delivery was reduced at rest (p < 0·05) but did not change during submaximal exercise. At rest both the mixed venous oxygen content and arteriovenous oxygen difference were reduced (fig 2A). During submaximal exercise the arteriovenous oxygen content was reduced by the same amount as the arterial oxygen content with no change in systemic oxygen delivery (fig 2B). There were no changes in the placebo group.

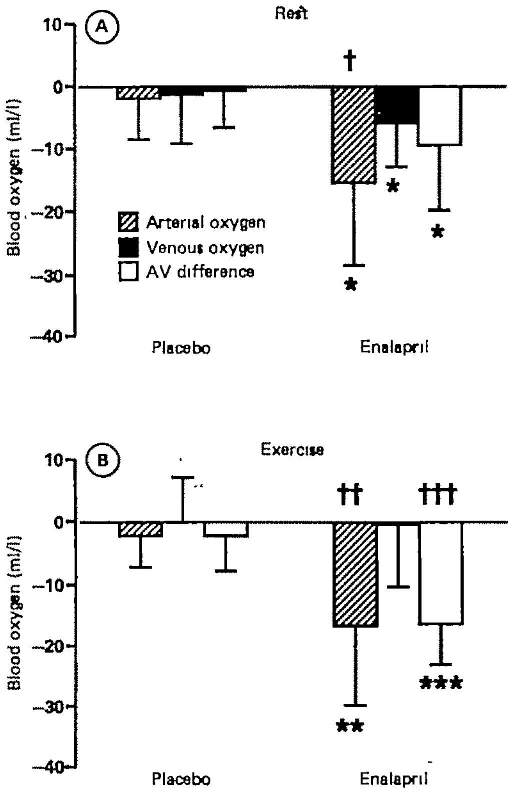


*Figure 2 Absolute changes (mean (SD)) in blood oxygen content, compared with baseline, at rest and during submaximal exercise. Differences within groups compared with baseline are indicated as *p < 0·05, **p < 0·01, and ***p < 0·001. Differences in changes from baseline between groups are indicated as †p < 0·05, ††p < 0·01, and †††p > 0·001.*

Oxygen uptake and arterial blood lactate remained unchanged in the two groups both at rest and during submaximal exercise. Plasma noradrenaline did not differ from baseline in the placebo group but was reduced both at rest and during submaximal exercise with enalapril (table 3).

Discussion

The present study showed that long term treatment with enalapril unloads the heart both at rest and during exercise, improves renal function, and induces a reduction in haemoglobin concentration and the total amount of haemoglobin in patients with stable, chronic, moderate heart failure caused by dilated cardiomyopathy. During submaximal exercise the reduction in arterial oxygen content counterbalanced the increased systemic blood flow and resulted in an unchanged delivery of systemic oxygen.

COMPARISON WITH PREVIOUS STUDIES

Several controlled long term studies of angiotensin converting enzyme inhibition in heart failure have reported symptomatic improvement.[3 18-20] However, the effect on exercise tolerance is variable. An increase in exercise duration compared with placebo[3 18-21] or with baseline in the treatment group[1 22] or lack of improvement[23-25] have been reported. If exercise tolerance increases gradually[18 21] a study period of less than 12 weeks may be too short to show that treatment increases exercise duration.[24 25] Increased daily activity resulting in peripheral conditioning may be important[26 27] and may explain the gradual improvement in exercise capacity. However, in the present long term study, both exercise duration and perceived exertion remained unchanged during

Exercise			
Placebo (n = 9)		*Enalapril (n = 8)*	
Baseline	*12 weeks*	*Baseline*	*12 weeks*
111 (20)	119 (25)	121 (22)	112 (17)***††
24 (12)	24 (13)	31 (10)	22 (7)***‡
96 (12)	102 (13)	106 (13)	91 (21)**‡
7·0 (1·5)	7·2 (1·3)	6·6 (1·3)	7·7 (1·8)*
1069 (295)	1118 (269)	1167 (172)	886 (202)**‡
152 (16)	151 (16)	159 (11)	147 (10)**‡
97 (1)	97 (1)	97 (2)	97 (2)
201 (21)	198 (24)	212 (17)	195 (15)**‡
11·5 (0·8)	11·3 (0·9)	12·2 (1·8)	12·6 (1·9)
10·3 (1·6)	10·4 (1·9)	10·4 (1·2)	10·5 (2·7)
1·7 (0·6)	2·1 (0·6)	2·1 (0·7)	2·0 (0·5)
4·6 (1·6)	6·0 (1·7)	6·4 (3·2)	4·7 (2·3)*††

the symptom limited maximal exercise test. Also, arterial blood lactate did not change during the submaximal exercise test. These findings indicate a lack of peripheral conditioning and a lack of increased oxidative capacity in working skeletal muscle. Our patients might have already conditioned themselves during routine daily activities to a high level of oxidative capacity in relation to their cardiac reserve. This would have limited their ability to improve their conditioning.

To date six double blind trials have reported haemodynamic effects both at rest and during exercise after long term angiotensin converting enzyme inhibition in heart failure. Important differences in study design make comparisons difficult. In three studies haemodynamic recordings were made with the patient in the supine position and at a submaximal workload[2 28 29] whereas in the other three studies recordings were made with the patient in the upright position and/or at peak exercise.[1 24 25] In half of the studies diuretics were withheld on the day of investigation.[1 28 29] In the present study enalapril significantly unloaded the heart, which must have reduced the metabolic cost for the left ventricle.[30] This finding is consistent with previous studies.[2 24 29] However, the highly significant changes from baseline in the present study suggest a more pronounced and beneficial haemodynamic response than in the earlier studies. Several factors could have contributed to these differences. Firstly, we used a higher daily dose of enalapril, which probably produced more complete converting enzyme inhibition than one in which only minor haemodynamic changes occurred.[29] Secondly, our patients were given diuretics on the day of investigation and this may have potentiated the effects of enalapril owing to complex interactions between the diuretics and converting enzyme inhibitors.[31] Thirdly, the reduction in haemoglobin concentration may lessen blood viscosity and total peripheral resistance.[32] Finally, during exercise, reduced arterial oxygen content may induce a compensatory vasodilatation in skeletal muscle[33] and thereby reduce systemic vascular resistance.

In previous studies the heterogeneity of patients—with heart failure or unstable vascular homoeostasis or both—and changes in plasma volume may have masked the effect of converting enzyme inhibition on haemoglobin concentration shown in this study. Furthermore, we studied our patients for long enough (probably a minimum of six weeks) to detect these changes. Similarly, rats treated with captopril showed a delay of recovery from haemorrhagic anaemia at six weeks.[34]

ERYTHROPOIESIS AND ANGIOTENSIN CONVERTING ENZYME INHIBITION

Erythropoietin regulates erythropoiesis and is mainly produced in the kidney.[4] A reduced renal oxygen supply in anaemia and hypoxic hypoxia or renal hypoperfusion or both elicit oxygen sensing reactions that have been postulated to trigger the release of several mediators such as adenosine, prostaglandins, and cyclic AMP. These messenger molecules may stimulate the synthesis and release of erythropoietin.[4] Also, changes in the ratio of renal oxygen demand to supply can affect erythropoietin release. Tubular sodium reabsorption is the predominant determinant of renal oxygen consumption.[35] Reduced erythropoietin formation in response to normobaric hypoxia after inhibition of sodium reabsorption in the proximal tubule has been reported in an experimental study.[36] This finding suggests that the function of the renal oxygen sensor is related to proximal tubular function.

Heart failure is characterised by increased plasma concentrations of noradrenaline which reflect increased overall sympathetic activity. Also, renal noradrenaline spillover is increased at rest and during exercise.[37] Increased renal nerve sympathetic activity stimulates intrarenal release of prostaglandins and activates the renin-angiotensin system.[38] Renal sympathetic nerves and angiotensin II interact functionally.[39] Both induce changes in the renal microcirculation, causing reduced renal blood flow and redistribution from the cortex to the medulla.[38] They may also directly and indirectly enhance sodium reabsorption by the proximal tubule.[40 41] Consequently, the oxygen supply/demand ratio may be altered in the renal cortex in heart failure. Such renal responses could stimulate erythropoietin production directly or indirectly. The reported high concentrations of erythropoietin in patients with congestive heart failure[42] support this concept.

Converting enzyme inhibitors reduced the production of angiotensin II, and this resulted in attenuated sympathetic activity[43 44] and an improved renal blood flow.[40] These effects were confirmed in the present study. Enalapril induced a reduction in plasma noradrenaline both at rest and during submaximal exercise, which is consistent with a previous controlled study.[44] This finding indicates reduced systemic, and probably also renal, sympathetic activity.[37] The glomerular filtration rate, as determined by endogenous creatinine clearance, increased and the renal plasma flow tended to increase. However, renal plasma flow was determined at rest and not during daily activities. This it is not as representative of the

24 hours as the endogenous creatinine clearance. Furthermore, both arterial oxygen pressure and arterial oxygen saturation were unchanged. Consequently, the attenuated erythropoiesis we saw after enalapril treatment may be due to changes in renal circulation and/or hormone production and their modulation of erythropoietin release. This hypothesis is supported by a recent study in which high serum erythropoietin concentrations returned to normal during enalapril treatment of congestive heart failure.[42]

Functional renal insufficiency was reported during angiotensin converting enzyme inhibition in up to one third of salt-restricted patients with severe chronic heart failure and with constant dosages of diuretics.[45] In two controlled studies Cleland and colleagues found that when sodium intake and diuretic dosage were kept constant the glomerular filtration fell considerably during treatment with captopril and enalapril.[19 20] In general their patients were not very hyponatraemic and they were not sodium restricted. Another large controlled study to compare lisinopril and captopril showed small increases in blood urea nitrogen and serum creatinine.[46] These findings indicate that it is usual to see a fall in glomerular filtration rate when treatment with an angiotension converting enzyme inhibitor is started, but that in certain instances, as in the present study, this may not occur. In uncontrolled studies others reported little change or increases in the glomerular filtration rate when the dosage of diuretics was reduced or when the sodium intake was unrestricted.[47–49] Similarly, in the present study, the improvement in the glomerular filtration rate in the enalapril group was attributable to the improvements in the three patients in whom the dose of diuretics was reduced.

Transient weight gain and plasma volume expansion have been reported soon after the start of treatment with converting enzyme inhibition.[19 20 50] However, during long term treatment there may be a progressive reduction in plasma volume.[50] In the present study plasma volume remained unchanged after 12 weeks, indicating that the reduction in haemoglobin concentration was not caused by plasma volume expansion.

In conclusion, the present study showed the complexity of the effects of angiotensin converting enzyme inhibition in heart failure. Enalapril unloaded the heart and improved renal function and the systemic blood flow. The increased systemic blood flow was, however, counterbalanced by an adaptive reduction in haemoglobin concentration and arterial oxygen carrying capacity, which resulted in an unchanged systemic oxygen delivery during submaximal exercise. Further, our findings underscore the importance of evaluating the effect of angiotensin converting enzyme inhibition in heart failure on haemoglobin concentration in haemodynamic long term intervention studies to avoid the effect on systemic or regional oxygen delivery being overestimated.

This study was supported by the Swedish Heart and Lung Foundation and the Swedish Medical Research Council.

1 Kramer BL, Massie BM, Topic N. Controlled trial of captopril in chronic heart failure, a rest and exercise hemodynamic study. *Circulation* 1983,67:807–16.

2 Bussman WD, Storger H, Hadler D, Reifart N, Fassbinder W, Jungmann E, *et al*. Long-term treatment of severe chronic heart failure with captopril: a double-blind, randomized, placebo-controlled, long-term study. *J Cardiovasc Pharmacol* 1987;9(suppl 2):S50–60.

3 Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. *Circulation* 1984;70:271–8

4 Eckardt KU, Bauer C. Erythropoietin in health and disease. *Eur J Clin Invest* 1989;19:117–27.

5 Fisher JW, Samuels AI, Langston JW. Effects of angiotensin and renal artery constriction on erythropoietin production. *J Pharmacol Exp Ther* 1967;157.618–25.

6 Gould AB, Goodman S, DeWolf R, Onesti G, Swartz C Interrelation of the renin system and erythropoietin in rats. *J Lab Clin Med* 1980,96:525–34.

7 Fried W, Barone-Varelas J, Barone T, Anagnostuo A. Effect of angiotensin infusion on extrarenal erythropoietin production. *J Lab Clin Med* 1982;99·520–5.

3 Hirakata H, Onoyama K, Hori K, Fujishima M. Participation of the renin-angiotensin system in the captopril-induced worsening of anemia in chronic hemodialysis. *Clin Nephrol* 1986;26:27–32

9 Griffing GT, Melby JC. Enalapril (MK-421) and the white cell count and haematocrit [letter]. *Lancet* 1982;i:1361.

10 Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. *Am J Cardiol* 1972;30:757–62.

11 Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography. results of a survey of echocardiographic measurements. *Circulation* 1978;58·1072–83

12 Jonsell S. A method for the determination of the heart size by teleroentgenography (a heart volume index). *Acta Radiologica* 1939;20:325–40.

13 Borg GAV. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14:377–81.

14 Karlsson J, Jacobs I, Sjodin P, Tesch P, Kaiser P, Sahl O, *et al*. Semi-automatic blood lactate assay· experiences from an exercise laboratory. *Int J Sports Med* 1983,4:52–5.

15 Hallman H, Farnebo LO, Hamberger B, Jonsson G. A sensitive method for determination of plasma catecholamines using liquid chromatography with electrochemical detection. *Life Sci* 1978;23:1049–52.

16 Rustad H. Correction for trapped plasma in microhematocrit determinations. *Scand J Clin Lab Invest* 1964, 16 677–9.

17 Holmgren A, Ekelund LG. Determination of total blood volume In: Sjöstrand T, ed. *Clinical physiology*. Stockholm: Svenska Bokförlaget, 1967:241–5.

18 Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure *J Am Coll Cardiol* 1983;2 755–63.

19 Cleland JGF, Dargie HJ, Ball SG, Gillen G, Hodsman GP, Morton JJ, *et al*. Effects of enalapril in heart failure: a double-blind study of effects on exercise performance, renal function, hormones, and metabolic state. *Br Heart J* 1985,54:305–12.

20 Cleland JGF, Dargie HJ, Hodsman GP, Ball SG, Robertson JIS, Morton JJ, *et al*. Captopril in heart failure: a double-blind controlled trial. *Br Heart J* 1984,52:530–5

21 Creager MA, Massie BM, Faxon DP, Friedman SD, Kramer BL, Weiner DA, *et al*. Acute and long-term effects of enalapril on the cardiovascular response to exercise and exercise tolerance in patients with congestive heart failure. *J Am Coll Cardiol* 1985;6:163–7.

22 Franciosa JA, Wilen MM, Jordan RA. Effects of enalapril, a new angiotensin-converting enzyme inhibitor, in a controlled trial in heart failure *J Am Coll Cardiol* 1985;5:101–7.

23 McGrath BP, Arnolda L, Matthews PG, Jackson B, Jennings G, Kiat H, *et al*. Controlled trial of enalapril in congestive heart failure. *Br Heart J* 1985;54.405–14.

24 Mulligan IP, Fraser AG, Tirlapur V, Lewis MJ, Newcombe RG, Henderson AH. A randomized cross-over study of enalapril in congestive heart failure; haemodynamic and hormonal effects during rest and exercise. *Eur J Clin Pharmacol* 1988;34:323–31.

25 Timmis AD, Bojanowski LM, Najm YC, Nelson DJ, Gosling RG. Captopril versus placebo in congestive heart failure: effects on oxygen delivery to exercising skeletal muscle. *Eur Heart J* 1987;8:1295–304.

26 Sinoway LI, Minotti JR, Davis D, Pennock JL, Burg JE, Musch TI, *et al*. Delayed reversal of impaired vasodilatation in congestive heart failure after heart transplantation. *Am J Cardiol* 1988;61·1076–9

27 Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metabolic effects. *Circulation* 1988;78:506–15.

Drexler H, Banhardt U, Meinertz T, Wollschlager H, Lehmann M, Just H. Contrasting peripheral short-term and long-term effects of converting enzyme inhibition in patients with congestive heart failure. A double-blind, placebo-controlled trial *Circulation* 1989;79:491–502

29 Webster MWI, Fitzpatrick MA, Hamilton EJ, Nicholls MG, Ikram H, Espiner EA, *et al*. Effects of enalapril on clinical status, biochemistry, exercise performance and haemodynamics in heart failure. *Drugs* 1985;30(suppl 1):74–81.

30 Cohn JN, Mashiro I, Levine TB, Mehta J. Role of vasoconstrictor mechanisms in the control of left ventricular performance of the normal and damaged heart. *Am J Cardiol* 1979,44:1019–22

31 Cleland JGF, Gillen G, Dargie HJ. The effects of frusemide and angiotensin-converting enzyme inhibitors and their combination on cardiac and renal haemodynamics in heart failure. *Eur Heart J* 1988,9:132–41.

32 Fan FC, Chen RYZ, Schuessler GB, Chien S Effects of hematocrit variations on regional hemodynamics and oxygen transport in the dog. *Am J Physiol* 1980;238: H545–52.

33 Saltin B, Kiens B, Savard G, Pedersen PK. Role of hemoglobin and capillarization for oxygen delivery and extraction in muscular exercise *Acta Physiol Scand* 1986; 128(suppl 556):21–32.

34 Onoyama K, Motomura K, Makita H, Kiyama S, Takata Y, Urabe A, *et al* Effects of long-term captopril on angiotensin II and erythropoietin levels and recovery from hemorrhagic anemia in rats. *Curr Ther Res* 1987;41: 472–7.

35 Bauer C, Kurtz A. Oxygen sensing in the kidney and its relation to erythropoietin production *Annu Rev Physiol* 1989;51:845–56.

36 Eckardt KU, Kurtz A, Bauer C. Regulation of erythropoietin production is related to proximal tubular function. *Am J Physiol* 1989;256:F942–7

37 Hasking GJ, Esler MD, Jennings GL, Dewar E, Lambert G. Norepinephrine spillover to plasma during steady-state supine bicycle exercise. *Circulation* 1988;78:516–21.

38 Osborn JF, Johns EJ. Renal neurogenic control of renin and prostaglandin release. *Miner Electrolyte Metab* 1989;15. 51–8.

39 Ichikawa I, Kon V, Pfeffer MA, Pfeffer JM, Brenner BM Role of angiotensin II in the altered renal function of heart failure. *Kidney Int* 1987;31 S213–5.

40 Cleland JGF, Dargie HJ. Heart failure, renal function, and angiotensin converting enzyme inhibitors. *Kidney Int* 1987;20·S220–8.

41 Hall JE. Control of sodium excretion by angiotensin II· intrarenal mechanisms and blood pressure regulation. *Am J Physiol* 1986;250:R960–72.

42 Fyhrquist F, Karppinen K, Honkanen T, Saijonmaa O, Rosenlöf K High serum erythropoietin levels are normalized during treatment of congestive heart failure with enalapril. *J Intern Med* 1989,226·257–60.

43 Antonnacio MJ, Kerwin L Evidence for prejunctional inhibition of norepinephrine release by captopril in spontaneously hypertensive rats. *Eur J Pharmacol* 1980; 68.209–12.

44 McGrath BP, Arnolda LF Enalapril reduces the catecholamine response to exercise in patients with heart failure *Eur J Clin Pharmacol* 1986;30:485–7.

45 Packer M, Lee WH, Medina N, Yushak M, Kessler PD Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. *Ann Intern Med* 1987;106.345–54.

46 Giles TD, Katz R, Sullivan JM, *et al*. Short- and long-acting angiotensin-converting enzyme inhibitors: a randomized trial of lisinopril versus captopril in the treatment of congestive heart failure. *J Am Coll Cardiol* 1989,13: 1240–7.

47 Kubo S, Nishioka A, Nishimura H, Kawamura K, Takatsu T. Effects of captopril on arterial and venous pressure, renal function and humoral factors in severe chronic congestive heart failure *Clin Pharmacol Ther* 1984,36:456–63.

48 Dzau VJ, Hollenberg NK. Renal response to captopril in severe heart failure: role of furosemide in natriuresis and reversal of hyponatremia. *Ann Intern Med* 1984,100 777–82.

49 Mujais SK, Fouad FM, Textor SC, Tarazi RC, Bravo EL, Hart N, *et al*. Transient renal dysfunction during initial inhibition of converting enzyme in congestive heart failure. *Br Heart J* 1984,52:63–71.

50 Fouad FM, Tarazi RC, Bravo EL, Hart NJ, Castle LW, Salcedo EE Long-term control of congestive heart failure with captopril. *Am J Cardiol* 1982,49 1489–96.

Br Heart J 1991;66:206–11

Differences in first dose response to angiotensin converting enzyme inhibition in congestive heart failure: a placebo controlled study

R J MacFadyen, K R Lees, J L Reid

Abstract

Objective—To compare the first dose responses to low dose angiotensin converting enzyme inhibitors (captopril, enalapril, and perindopril) in elderly patients with stable chronic heart failure.

Design—Double blind, randomised, placebo controlled, parallel, group prospective study of elderly patients with stable chronic heart failure.

Setting—General hospital in-patient admissions for supervised diuretic withdrawal (24–48 hours) and the introduction of angiotensin converting enzyme inhibitor therapy.

Patients—48 unselected elderly (58–85 years) patients with symptomatic but stable chronic heart failure (New York Heart Association grades II–IV) confirmed by clinical history, examination, and cardiological investigations. Patients gave their written and informed consent to receive their initial treatment under double blind conditions; blood pressure was monitored and blood samples taken to measure the pharmacokinetic and neurohormonal responses.

Intervention—Patients were randomised to receive a daily oral dose of placebo, captopril (6·25 mg), enalapril (2·5 mg), or perindopril (2 mg).

Main outcome measures—Blood pressure and heart rate responses, drug concentration, and plasma renin and ACE activities. Differences between treatment groups were analysed by analysis of variance.

Results—The four randomised groups of patients had similar age, severity of heart failure (NYHA class), pretreatment diuretic dosage, plasma renin activity, and serum electrolyte state. Placebo treatment caused a modest but significant diurnal fall in blood pressure. Captopril produced a significant early (1·5 hours) and brief fall in blood pressure. The blood pressure fall with enalapril was later (4–10 hours), longer lasting, and was associated with significant slowing of supine heart rate. Though perindopril produced a similar plasma ACE inhibition to that produced by enalapril, it only caused changes in blood pressure that were similar to those caused by placebo.

Conclusions—This controlled study is the first to indicate a qualitative difference in the acute response to angiotensin converting enzyme inhibitors with similar structure and metabolism (that is, enalapril and perindopril). Low dose perindopril seems to be less likely to cause hypotension in patients with heart failure. The explanation for the differences is unclear but may reflect differential effects on local tissue angiotensin generation.

University Department of Medicine and Therapeutics, University of Glasgow
R J MacFadyen
K R Lees
J L Reid

Correspondence to
Dr R J MacFadyen,
University Department of Medicine and Therapeutics,
Gardiner Institute, Western Infirmary, Glasgow
G11 6NT

Accepted for publication
25 March 1991

Several angiotensin converting enzyme (ACE) inhibitors have been shown to be valuable in the management of chronic heart failure.[1-4] They relieved symptoms, improved haemodynamic function, and reduced the associated mortality regardless of the aetiology of the syndrome. Efficacy has been well documented for moderate to severe chronic heart failure (New York Heart Association (NYHA) grades III–IV) and more recent studies suggest benefit in milder disease.[5] In most instances treatment with ACE inhibitors has been studied as an adjunct to diuretic and in some instances digoxin treatment. A series of case reports and small studies showed a considerable fall in blood pressure in response to the first dose of ACE inhibitor in patients with mild heart failure.[6] The origins of this response remain unclear. It may partly reflect activation of the circulating and tissue based renin angiotensin system either as a response to chronic heart failure[7] or to preceding or concurrent diuretic treatment.[8] It may be an expression of the range of individual sensitivity or responsiveness to the drug and dose used. Some workers have highlighted the role of reflex vagally mediated hypotension occurring in these patients via the Bezhold-Jarisch reflex.[9] In view of this background, clinicians have empirically used hospital admission for supervised treatment, dose reduction, variable periods of diuretic withdrawal, and blood pressure monitoring.[10]

Non-invasive, placebo controlled, comparative studies of the low doses currently used are rare. In addition, with the increasing range of ACE inhibitors the possibility of an agent specific element to this hypotensive response has not been adequately considered. We have conducted a randomised, double blind, parallel group study in elderly patients with stable chronic heart failure who were routinely admitted to hospital for supervised diuretic withdrawal and initiation of treatment with ACE inhibitors. We compared the responses to low oral doses of three agents and placebo.

Patients and methods

A single dose randomised, double blind, placebo controlled, parallel group study was conducted in 48 unselected elderly (58–85 years) patients admitted to hospital for supervised initiation of treatment with an ACE inhibitor. We selected patients with chronic heart failure who were symptomatic on diuretic treatment (generally >80 mg frusemide or equivalent/day). None had an important fluid imbalance by clinical criteria nor an acute decompensation in the preceding three months. The diagnosis was confirmed by clinical history and by physical, radiological, and electrocardiographic examination before treatment. Many patients also underwent echocardiography or radionuclide scanning, or had been investigated by cardiac catheterisation. All patients had stable renal function and normal serum sodium (⩾135 mmol/l) before treatment.

Four study groups (n = 12) were given oral captopril 6·25 mg, oral enalapril 2·5 mg, oral perindopril 2 mg, or oral placebo (lactose) within an opaque gelatin capsule. Table 1 shows the characteristics of the four groups. The study protocol was approved by the local research and ethics review committee. All patients gave their written and informed consent to take part in the study.

PROCEDURE

Diuretic treatment was withdrawn for 24–48 hours before treatment and in most this was 48 hours. Concomitant treatment with vasoactive agents was stopped on the day of study and was not resumed until after non-invasive haemodynamic monitoring was complete 24 hours after dosing with ACE inhibitor or placebo. Digoxin, where prescribed, was continued unaltered. On the morning of the study (at about 07 30 hours) a heparinised peripheral venous cannula was inserted in an antecubital vein to take blood samples. Blood pressure was recorded (Sentron, Bard, Sunderland, UK) automatically every two minutes while the patients had a light breakfast and rested supine for at least 30 minutes before treatment. Baseline blood pressure was established over this period. After the period of rest venous blood was drawn for baseline determinations of plasma ACE and renin activities, routine biochemistry, haematology, and serum drug concentration. Oral treatments were administered double blind in their standard formulations within an opaque gelatin capsule prepared in accordance with the randomisation schedule held by the department of pharmacy.

Table 1 Characteristics of patients

	Placebo (n=12)	*Captopril (n=12)*	*Enalapril (n=12)*	*Perindopril (n=12)*
M:F (n)	11:1	8·4	6·6	6:6
Age (mean (1 SD)) (yr)	68 2 (5 7)	67 8 (5 6)	65 9 (7·3)	69 2 (7 9)
NYHA class				
II	3	6	4	3
III	9	5	8	9
IV	—	1	—	—
Aetiology of CCF				
Ischaemic heart disease	6	7	6	4
Alcohol related cardiomyopathy	1	—	—	—
Dilated cardiomyopathy	1	—	3	3
Valvar heart disease	—	1	—	—
Combinations of above	4	4	3	5
Atrial fibrillation	2	2	—	3

CCF, chronic heart failure

After oral dosing blood pressure was measured in supine patients every 2 minutes with additional triplicate determinations at set time points. Blood samples were withdrawn frequently to determine the pharmacokinetic profile, ACE activity, and renin activity. Patients remained supine and received their normal meals throughout the study until 10 hours after dosing. Then they were allowed to rise but they were supine for at least 45 minutes before further blood sampling and blood pressure recordings at 24 hours after dosing. After this the nature of treatment was decoded and further treatment was arranged including re-instatement of diuretics and vasodilators at the discretion of the clinical staff. Patients receiving placebo continued on diuretic withdrawal and received open captopril with conventional observation on the ward. These patients were not included in any other active treatment group.

LABORATORY AND STATISTICAL ANALYSIS

We used high pressure liquid chromotography to measure the drug concentration and plasma ACE activity from the production of hippuric acid released from the exogenous substrate Hip-His-Leu.[11] Owing to the special sample preparation required with captopril to avert in vitro dimer formation and dissociation from ACE neither drug concentrations nor ACE activity could be assessed in the captopril group. Plasma renin activity was assessed by generation of angiotensin II from exogenous angiotensin I measured by radioimmunoassay.[12] The mean of triplicate mean arterial blood pressure (BP) (diastolic BP + ((systolic BP − diastolic BP)/3)) and heart rate recordings was used for statistical analysis both as absolute values and as changes from baseline. Repeated measures analysis of variance was applied, followed where appropriate by multiple *t* testing using Bonferroni correction for treatment effects at given time points. Effects with a p value <0·05 were regarded as significant. Data are shown as mean (1 SD). Biochemical indices were compared by one way ANOVA, and NYHA class was compared by Kruskal-Wallis ANOVA by ranks. Plasma renin activity was compared after logarithmic transformation.

Results

GENERAL

Each of the parallel groups contained patients of a similar age distribution, NYHA class, and

Table 2 Summary of comparisons for pre and post treatment laboratory data, age, and NYHA class

	Placebo		*Captopril*		*Enalapril*		*Perindopril*		*ANOVA p =*
Age	−68·2	(5·7)	67·8	(5·6)	65·9	(7·3)	69·2	(7·9)	0·677
Na^+	138·9	(2·5)	141·2	(3·4)	140·3	(2·7)	140·8	(2·4)	0·220
ΔNa^+	−0·2	(2·8)	+0·1	(2·3)	−0·5	(2·1)	+0·3	(1·2)	0·794
K^+	4·1	(0·6)	4·2	(0·3)	4·2	(0·6)	3·9	(0·6)	0·407
ΔK^+	+0·02	(0·6)	−0·15	(0·4)	+0·05	(0·6)	+0·08	(0·4)	0·684
Urea	8·5	(5·9)	6·3	(1·7)	7·2	(2·5)	8·6	(3·2)	0·380
Δ urea	−1·4	(4·0)	−0·1	(1·1)	−0·4	(1·3)	−0·4	(1·8)	0·570
Creatinine	107	(15)	98	(22)	102	(29)	122	(36)	0·150
Δ creatinine	−0·6	(19)	−4·0	(12)	−8·2	(16)	−6·6	(15)	0·651
Hb	14·4	(1·3)	13·5	(1·4)	14·0	(1·2)	13·8	(1·1)	0·408
Δ Hb	−1·2	(0·6)	−1·2	(0·5)	−1·8	(0·5)	−1·2	(0·5)	0·016
NYHA (average rank)	26·7		21·3		24·0		26·0		0·681*

*Kruskal-Wallis.

baseline laboratory variables. None of the laboratory indices was significantly altered by treatment in any of the parallel groups with the exception of a modest fall in haemoglobin which we have previously seen and attributed to blood sampling (table 2). No patient experienced important symptoms during diuretic withdrawal or the study period and all left hospital without ill effect after adjustment of diuretic dosage and of other drugs.

HAEMODYNAMIC FUNCTION

There were differences between the groups in the pretreatment baseline blood pressure and heart rate values. Baseline mean arterial pressure was significantly higher ($p < 0.05$) in the group treated with enalapril (106·4 (11·6) mm Hg) than in those who received captopril (98·4 (10·8)), perindopril (98·2 (11·0)), or placebo (100·3 (12·8)). In addition, the baseline supine heart rate was significantly lower ($p < 0.05$) in the group who were treated with captopril (75·9 (9·8) beats/minute) than in those who received enalapril (83·3 (15·9)), perindopril (77·1 (10·4)), or placebo (81·1 (12·8)). For these reasons the temporal pattern of response was described as the change from individual baseline pressures and heart rate rather than absolute values. This did not materially alter the general trends and the statistically significant differences.

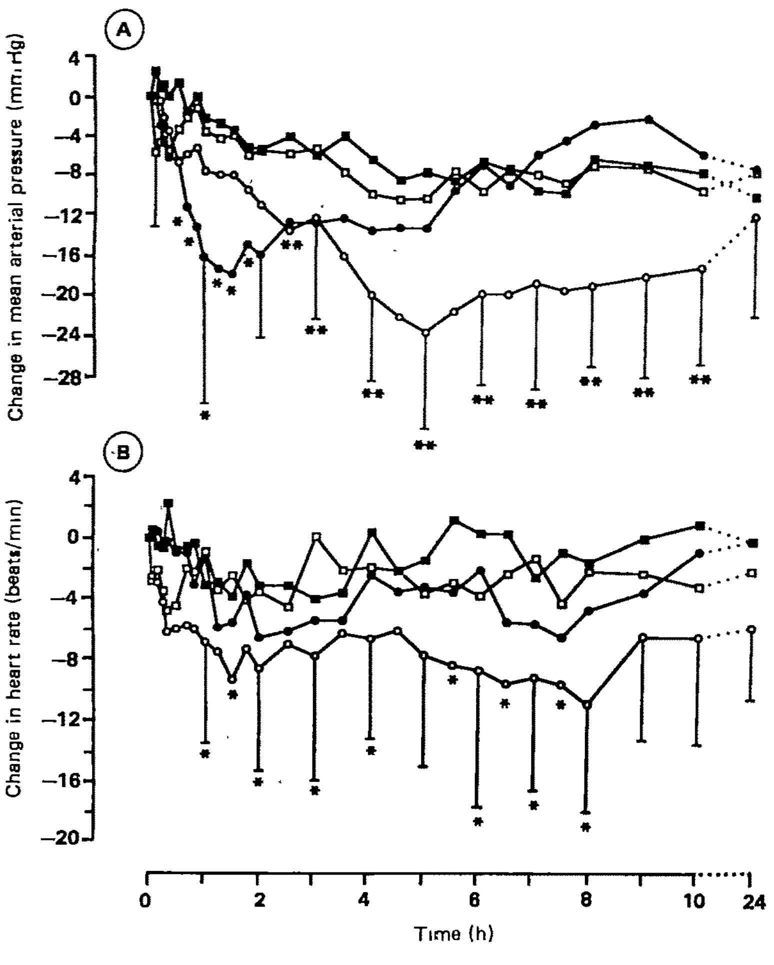


Figure 1 Baseline-corrected mean effect (1 SD) of oral placebo (□), captopril 6·25 mg (●), enalapril 2·5 mg (○), or perindopril 2 mg (■) on supine mean arterial pressure (A) and heart rate (B) in patients with chronic heart failure.

Mean arterial pressure fell during placebo treatment by approximately 10 mm Hg over the first 4·5 hours. Compared with the other treatments, captopril produced a significant fall in blood pressure (trough at 1·5 hours). Blood pressure had largely returned to normal by six hours. Enalapril produced a smooth and protracted fall in mean arterial pressure that was significantly greater than that produced by placebo from two to five hours (maximum at four to five hours post-dosing). Pressure remained significantly depressed at 10 hours. In contrast, after perindopril the mean arterial pressure did not significantly differ from placebo throughout the period of study (fig 1A). The individual maximum fall in mean arterial pressure from baseline was calculated. The mean maximum fall in the perindopril group (−15·1 (8·2), range −2 to −30·1 mm Hg) was similar to that seen with placebo (−16·4 (7·7), range −4 to −31·9 mm Hg). The mean maximum fall in mean arterial pressure for both the captopril (−22·4 (11·6), range −14 to −45·7) and enalapril (−26·4 (7·5), range −13·8 to −43) groups was significantly greater ($p = 0.012$).

Baseline corrected changes in mean supine heart rate were small in absolute terms. However, the group treated with enalapril showed a significant fall between one and eight hours after dosing (−10·8 (7·2) beats/minute) compared with placebo (−2·0 (9·6) beats/minute). This was not evident with captopril or perindopril (fig 1B).

ACE ACTIVITY AND RENIN AND DRUG CONCENTRATIONS

Pretreatment plasma renin activity (geometric mean, 95% confidence interval) after 24–48 hours of diuretic withdrawal was similar in all groups ($p = 0.183$, one way ANOVA); captopril group (1·1, 0·2 to 3·8 ng AI/ml/h) compared with placebo (3·2, 0·5 to 11·7), enalapril (1·7, 0·5 to 44·7), and perindopril (2·5, 0·2 to 11·9). There was no significant difference ($p = 0.222$ Kruskal-Wallis ANOVA) in the prestudy dose of diuretic drugs (mg frusemide/day) between those patients who received captopril (93 (33)), enalapril (85 (38)), perindopril (120 (40)), or placebo (110 (61)). All three active treatments increased plasma renin activity. The early rise associated with captopril was small because the initial sample was taken two hours after dosing. Enalapril and perindopril caused rises later (fig 2).

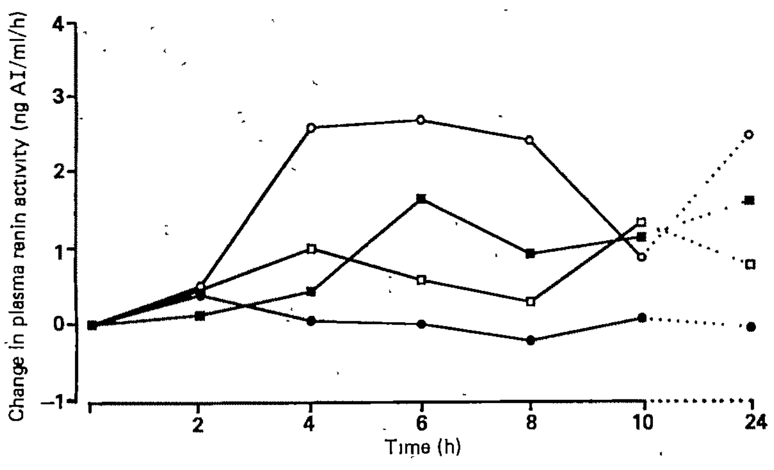


Figure 2 Plasma renin activity (geometric mean value) after oral placebo (□), captopril (●), enalapril (○), or perindopril (■).

Plasma ACE activity was significantly lower in both the perindopril and enalapril groups than in the placebo group (fig 3). Maximum ACE inhibition was similar in both active treatment groups (enalapril 63% and perindopril 68%) eight hours after dosing. The onset of inhibition was earlier with perindopril. Inhibition was significantly greater between 50 minutes and three hours after perindopril than after enalapril. After perindopril ACE inhibition was also significantly greater at 24 hours after dosing.

Figure 4 shows the pharmacokinetic profiles for the enalapril and perindopril groups. Concentrations of both the parent ester and active diacid metabolite were higher for enalapril than for perindopril. The mean (1 SD) time to peak ester concentrations (t_{max}) was 1·95 (0·7) hours for enalapril and 1·74 (0·7) hours for perindopril. The mean time to peak enalaprilat concentration was 6·9 (2·0) hours and that for perindoprilat was 5·48 (2·9) hours. In neither instance was there a significant difference between the groups in t_{max} for either ester ($p = 0·684$) or diacid ($p = 0·229$) (Kruskal-Wallis ANOVA). Generally speaking both treatments were associated with prolonged plateau concentrations of the active diacid.

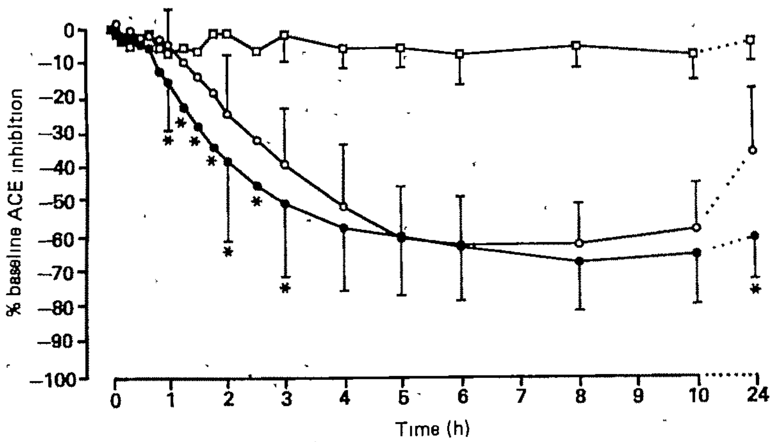


Figure 3 Plasma ACE inhibition (% baseline activity, enzyme units/ml, mean (1 SD)) after placebo (□), enalapril (○), or perindopril (●).

Discussion

We found significant differences in the responses to the recommended low doses of ACE inhibitors in elderly patients with chronic heart failure during temporary diuretic withdrawal. The use of a placebo controlled, randomised, parallel group design in this study allowed us to compare drug effects. To control for diurnal changes and feeding patterns,[13] it is important to compare the haemodynamic responses in these patients with those of a placebo treated group. We chose a parallel group design to avoid a carryover effect caused by the protracted elimination phase associated with some ACE inhibitors[14] and to avoid delay in the initiation of active treatment.

The first dose hypotensive response to ACE inhibitors in chronic heart failure has received much attention in case reports and small series. It has been reported to be associated with transient renal hypoperfusion damage.[15] However, the mechanism and significance of the response in clinical practice remain obscure. The relation of blood pressure fall to previous or concurrent diuretic therapy, the dose or type of ACE inhibitor used, and the importance of the range of individual patient responses are poorly defined. We chose to compare the degree and pattern of blood pressure response in the group of patients that we considered to be at greatest risk of developing a hypotensive response—elderly, diuretic treated patients with moderate to severe heart failure.

Though we used the standard low doses of both captopril and enalapril both these drugs caused falls in blood pressure consistent with previous reports. If, as some workers suggest, the first dose blood pressure response is related to the prevailing activation of the renin angiotensin system, as predicted by circulating renin activity,[16] it might be that our observations are an underestimate of the general degree of response in the captopril treated group. Nevertheless, we documented predictable and significant supine blood pressure falls regardless of diuretic withdrawal and relatively (but not significantly) lower renin activity in this group. Experience with lower oral doses of captopril—for example, 1 mg[17]—is limited, but their formulation is compromised by chemical instability.[18] Patterns of test dosing with captopril have been suggested but the individual relevance of this strategy to subsequent responses to higher doses of the same or different agents has not been documented. Captopril is frequently selected on the empirical basis that if symptomatic hypotension and hypoperfusion were to occur their duration would at least be limited compared with longer acting drugs.[19] Our comparison between low dose captopril and enalapril confirms this pattern. We found that neither captopril nor enalapril caused symptoms or adverse changes in renal biochemistry.

In contrast, low dose perindopril was not associated with any change in blood pressure or heart rate, though it caused comparable plasma ACE inhibition which, if anything, was more prolonged than after enalapril. This may

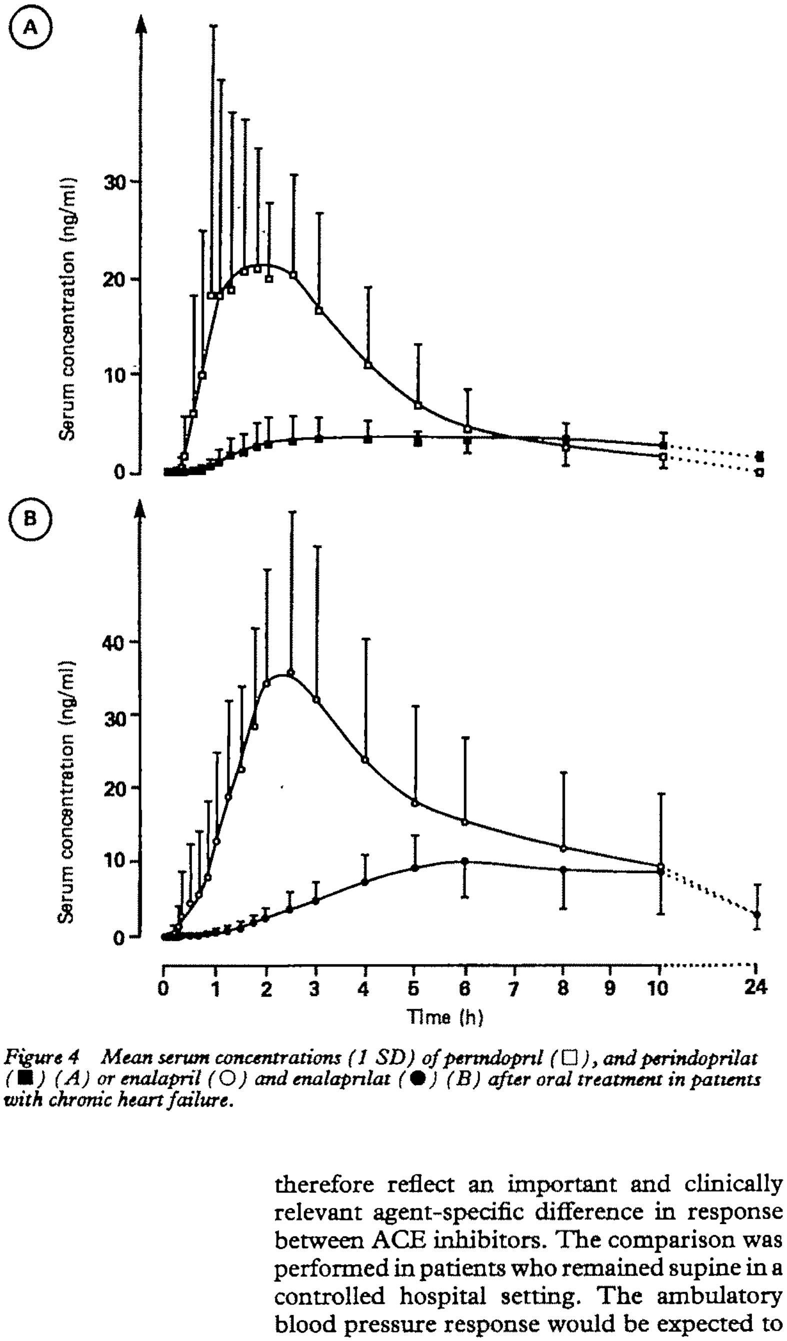


Figure 4 Mean serum concentrations (1 SD) of perindopril (□), and perindoprilat (■) (A) or enalapril (○) and enalaprilat (●) (B) after oral treatment in patients with chronic heart failure.

therefore reflect an important and clinically relevant agent-specific difference in response between ACE inhibitors. The comparison was performed in patients who remained supine in a controlled hospital setting. The ambulatory blood pressure response would be expected to follow a similar pattern. At the doses selected there was a similar differential response in heart rate. Altered autonomic tone and baroreceptor reflexes in patients in heart failure are well known[20] as are the antiadrenergic or parasympathomimetic properties of captopril,[21] enalapril,[22] and perindopril.[23] To our knowledge this is the first demonstration of a small but significant slowing of basal heart rate in a study of supine patients after low dose enalapril with an appropriate placebo control group. This effect on heart rate was seen only briefly with captopril and not seen at all with perindopril.

One of the proposed mechanisms for the fall in blood pressure in a proportion of heart failure patients treated with ACE inhibitors is activation of the Bezhold-Jarisch reflex by vagally mediated hypotension and bradycardia.[24] One of our patients had a considerable fall in blood pressure and associated bradycardia yet remained symptom free immediately after dosing with placebo (fig 5). He subsequently tolerated open captopril therapy on the following day without complications. His placebo response was not excluded from our analysis. This reflex mechanism may be relevant in a few reported cases of hypotension after ACE inhibitors in heart failure patients. The Bezhold-Jarisch reflex clearly has little relevance to specific ACE inhibitors, agent selection, or general management policies designed to avoid hypotension in heart failure because it is unpredictable and not related to dose or to individual drugs.

Studies with ACE inhibitors over the past 5–10 years have generated interest in the role of tissue based angiotensin generating systems with local autocrine or paracrine roles.[25] There is indirect evidence for such local systems in many tissues including heart, kidney, adrenal, brain, and blood vessels. Recent studies in animals with experimental heart failure suggest an activation of the tissue based angiotensin generating system.[26] However, there is as yet no direct evidence of the clinical significance of any tissue based renin angiotensin system to responses to ACE inhibitor drugs in man. In this acute study we found similar plasma ACE inhibition with both enalapril and perindopril yet the blood pressure responses were different. Differences in penetration and interaction with the tissue renin angiotensin systems may explain this finding. With both these drugs the net interaction with tissue and plasma ACE will be a product of the parent ester, a weak but lipid soluble ACE inhibitor, and the more potent but polar diacid metabolite. The potency ratios and polarity of ester and diacid vary substantially between different compounds despite a similar basic structure and there is limited in vitro evidence that the interaction is significant at least for plasma ACE.[27] At different tissue sites the bioavailability of each of these components would also be expected to vary and contribute further to potential differences in the pattern of tissue ACE inhibition. Because long term treatment involves the attainment of an equilibrium the most likely setting in which potential differences would be apparent is the first dose response.[28]

The interpretation of plasma ACE inhibition after chronic dosing with ACE inhibitor drugs is complicated by the coexistent reactive rise in renin activity. Moreover, substrate analysis of ACE activity may not give an absolute indication of circulating angiotensin peptide con-

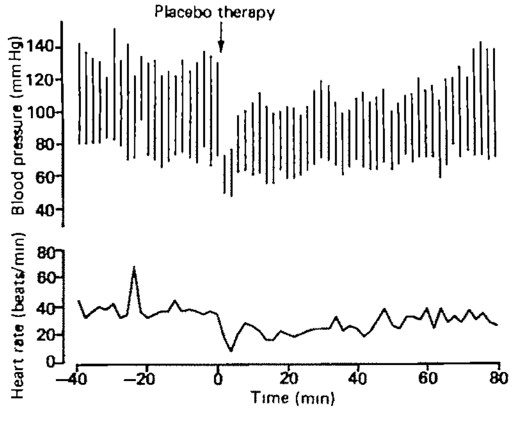


Figure 5 Individual blood pressure and heart rate profile of patient (case 27) on double blind placebo therapy.

centrations after chronic administration of different ACE inhibitors.[29] These factors are unlikely to be relevant to the acute responses described in heart failure patients in this study. In addition, they would not adequately explain the qualitative difference in blood pressure response between enalapril and perindopril.

Angiotensin converting enzyme is well known to be a non-specific metalloprotease and its inhibition has important interactions potentiating vasodilatatory prostaglandins and inhibiting the degradation of bradykinin. It is as yet unclear what these general interactions contribute to the cardiovascular effects of ACE inhibitors.[30] We are unaware of any experimental or clinical studies indicating the relevance of these interactions to the response to ACE inhibitors in heart failure. We think that the differential blood pressure responses observed are unlikely to be explained through differences in kinin or prostaglandin metabolism.

The significance of acute haemodynamic responses to ACE inhibitor drugs in patients with chronic heart failure is unclear. Pronounced responses are not markers of symptomatic benefit and, conversely, smaller blood pressure falls can be associated with benefit.[31] In general terms improvements in exercise duration and symptoms seem to require six to eight weeks of therapy and alternative mechanisms may be important in reducing mortality.[32] Because perindopril has been shown to provide symptomatic improvement in chronic heart failure,[4] similar to other ACE inhibitors, the lack of an initial blood pressure fall does not seem to be an indication of a lack of long term efficacy in heart failure. However, in acute heart failure perindopril may not share the haemodynamic benefits that have been shown with other ACE inhibitors.[33]

Our results indicate that clinically significant differences in responses to ACE inhibitor drugs can be observed in patients with chronic heart failure in a controlled hospital setting. Our study has general relevance because the patient population was not highly selected and because it included primarily the "high risk" groups of the elderly, diuretic pretreated patients with severe chronic heart failure. Any manoeuvre that reduces the risk of hypotensive responses in these patients may have clinical and possibly resource implications. The patient population, dose and agent used, and the adequate definition of haemodynamic and biochemical responses are important. Further study is required to define the explanation of the differences between the ACE inhibitors seen in our study.

We thank Dr F G Dunn, Dr W S Hillis (Stobhill Hospital), and Dr J A Kennedy (Western Infirmary, Glasgow) for allowing us to study their patients, Servier Laboratories (Slough, UK) for supplies of low dose perindopril, Mr G M Thomson and Ms L M Gilbert (Department of Pharmacy, Stobhill Hospital) for randomisation and preparation of treatments, and Mr J McCulloch and Mr D M Hughes for technical assistance. This study was supported by the British Heart Foundation.

1 Captopril Multicentre Research Group A placebo controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol* 1983,2.755–63

2 Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;316.1429–35

3 de Graef PA, Kingma JH, Duselman PHJN, Wesseling H, Lie KI. Acute haemodynamic and hormonal effects of ramipril in chronic congestive heart failure and comparison with captopril. *Am J Cardiol* 1987,59·164D–79D

4 Bounhoure JP, Bottineau G, Lechat P, Garnham J, Lapeyre G. Value of perindopril in the treatment of chronic congestive heart failure. *Clin Exp Hypertens [A]* 1989,11 (suppl 2):575–86

5 Riegger GAJ. ACE inhibitors in congestive heart failure. *Cardiology* 1989;76(suppl 2)·42–9

6 Cleland JGF, Dargie HJ, McAlpine H, Ball SG, Robertson JIS, Ford I. Severe hypotension after first dose of enalapril in heart failure. *BMJ* 1985,291 1309–12.

7 Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Edema of cardiac origin. studies of body water and sodium, renal function, hemodynamic indexes and plasma hormones in untreated congestive cardiac failure *Circulation* 1989,80 299–305

8 Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P Untreated heart failure clinical and neuroendocrine effects of introducing diuretics *Br Heart J* 1987,57.17–22

9 Semple PF, Thoren P, Lever AF Vasovagal reactions to cardiovascular drugs. the first dose effect *J Hypertens* 1988;6 601–6

10 McMurray J, Lang CC, Maclean DD, McDevitt DG, Struthers AD A survey of current use of angiotensin converting enzyme inhibitors by Scottish physicians in the treatment of chronic cardiac failure. *Scott Med J* 1989, 34:425–7.

11 Chiknas SG. A liquid chromatography assisted assay for angiotensin converting enzyme (peptidyl dipeptidase) in serum. *Clin Chem* 1979;25 1259–62

12 Derkx FHM, Tan-Tjiong HL, Man in't Veld AJ, Schalekamp MAP, Schalekamp MADH. Activation of inactive plasma renin by plasma and tissue kallikreins *Clin Sci* 1979,57:351–7

13 Packer M, Medina N, Yushak M. Haemodynamic changes mimicking a vasodilator drug response in the absence of drug therapy after right heart catheterisation in patients with chronic heart failure *Circulation* 1985,71:761–6

14 Belz GG, Kirch W, Kleinbloesem CH. Angiotensin converting enzyme inhibitors. relationship between pharmacodynamics and pharmacokinetics *Clin Pharmacokinet* 1988,15:295–318.

15 Mujais SK, Fouad FM, Textor SC, Tarazi RC, Bravo EL, Hart N, *et al* Transient renal dysfunction during initial inhibition of converting enzyme in congestive heart failure. *Br Heart J* 1984,52 63–71.

16 Packer M, Medina N, Yushak M, Lee WH Usefulness of plasma renin activity in predicting haemodynamic and clinical responses and survival during long term converting enzyme inhibition in severe chronic heart failure experience in 100 consecutive patients *Br Heart J* 1985; 54 298–304.

17 Warren SE, Smith HS, Janousek JP, Lanoue AS, Baim DS. Microdose captopril titration in chronic congestive heart failure *Heart Failure* 1986,2 185–9.

18 Colucci RD, Auty R, Scavone J, Glassner-Cohen L The chemical stability of captopril capsules *Int J Clin Pharmacol Ther Toxicol* 1989,27·599–601

19 Reid JL Angiotensin converting enzyme inhibitors in the elderly *BMJ* 1987,295 943–4.

20 Porter TR, Eckberg DL, Fritsch JM, Rea RF, Beightol LA, Schmedtje JF, *et al.* Autonomic pathophysiology in heart failure patients sympathetic cholinergic inter-relations *J Clin Invest* 1990,85 1362–71

21 Campbell BC, Sturani A, Reid JL. Evidence of parasympathomimetic activity of the angiotensin converting enzyme inhibitor, captopril in normotensive man *Clin Sci* 1985,68 49–56

22 Boni E, Alicandri C, Fariello R, Zaninelli A, Cantalamessa A, Corda L, *et al* Effect of enalapril on parasympathetic activity *Cardiovasc Drugs Ther* 1990,4 265–8

23 Ajayi AA, Lees KR, Reid JL Effects of the angiotensin converting enzyme inhibitor, perindopril, on autonomic reflexes. *Eur J Clin Pharmacol* 1986,30 177–82.

24 Mark AL The Bezhold-Jarisch reflex revisited. clinical implications of inhibitory reflexes originating in the heart. *J Am Coll Cardiol* 1983;1 90–102.

25 Ace inhibitors and tissue binding [editorial]. *Lancet* 1990, ii 718–20

26 Fabris B, Jackson B, Kohzuki M, Perich R, Johnston CI Increased cardiac angiotensin converting enzyme in rats with chronic heart failure. *Clin Exp Pharmacol Physiol* 1990;17 309–14

27 Harrigan JR, Hughes DM, Meredith PA, Reid JL Characterisation of the effects of prodrug concentration on the in vitro potency of metabolites of five ACE inhibitors [Abstract] *Eur J Clin Pharmacol* 1989,36(suppl) A186

28 Lees KR, MacFadyen RJ, Reid JL Tissue angiotensin converting enzyme inhibition relevant to clinical practice? *Am J Hypertens* 1990,3(Pt 2).266S–72S

29 Juillerat L, Nussberger J, Menard J, Mooser V, Christen Y, Waeber B, *et al* Determinants of angiotensin II generation during converting enzyme inhibition *Hypertension* 1990,16 564–72

30 Erdos EG Angiotensin I converting enzyme and the changes in our concepts through the years Lewis K Dahl Memorial Lecture. *Hypertension* 1990,16 363–70

31 Massie BM, Kramer BL, Topic N. Lack of relationship between the short term haemodynamic effects of captopril and subsequent clinical responses *Circulation* 1984,69 1135–41.

32 Packer M, Gottlieb SS, Blum MA Immediate and long term pathophysiologic mechanisms underlying the genesis of sudden cardiac death in patients with congestive heart failure *Am J Med* 1987,82(suppl 3A) 4–10

33 Flynn K, Coughlan MG, Phelan DM, Luke D, Neligan M, Wood AE Intravenous captopril in acute heart failure. *Lancet* 1988,i 173–4

Br Heart J 1991;66:212–6

Cyclosporin treatment does not impair the release of nitric oxide in human coronary arteries

Gregory S O'Neil, Adrian H Chester, Sudhir Kushwaha, Marlene Rose,
Samad Tadjkarimi, Magdi H Yacoub

Abstract

Objective—**It has been hypothesised that compromised endothelial function can contribute to the toxic manifestations associated with cyclosporin therapy. In vitro animal studies have implicated inhibition of release of the endothelium derived relaxing factor, nitric oxide; however, this has not been investigated in human tissue. The present study investigated the effect of cyclosporin A on nitric oxide release in human coronary arteries.**

Design—**Study of in vitro organ bath preparations and in vivo angiographic measurements in the coronary circulation.**

Patients—**For the in vitro experiments coronary arteries were harvested from the excised hearts of 10 patients requiring transplantation for reasons other than ischaemic heart disease. Three of these patients were being re-transplanted for obliterative bronchiolitis and had been receiving cyclosporin for a mean of 22 months. The in vivo study was performed on a group of 12 cardiac transplant recipients who were clinically well 1–5 years postoperatively and were not undergoing allograft rejection at the time of assessment.**

Results—**Isolated vessel segments in vitro relaxed in a dose dependent manner in response to substance P (10^{-11}–10^{-7} mol/l). The maximum response was 76·6 (7·4)% of the response to 1 μg/ml glyceryl trinitrate. Incubation with 1000 and 2000 ng/ml cyclosporin reduced the response to 63·0 (11·5)% and 62·2 (11·1)% respectively; this was not statistically significant. In segments taken from the explanted hearts of three patients requiring re-transplantation, the mean maximum response was 78·0 (11·0)% and there was no correlation between maximum response in segments from each patient and the duration of cyclosporin therapy. The effect of intracoronary substance P in 12 cardiac transplant recipients was also examined (mean cyclosporin blood concentration 228·9 (42·8) ng/ml). The mean maximum dilatations measured as the percentage diameter change induced by substance P and isosorbide dinitrate were 22·1 (3·2)% and 26·0 (2·5)% respectively. There was no correlation between the degree of endothelium mediated vasodilatation in response to substance P and cyclosporin concentration.**

Conclusions—**The nitric oxide response was preserved in the coronary arteries of patients exposed to cyclosporin. The mechanisms that initiate cyclosporin associated toxicity remain to be elucidated.**

The outcome in patients after heart transplantation has been considerably improved by cyclosporin therapy.[1] None the less, several cyclosporin associated toxic manifestations have been encountered, particularly hypertension[2-4] and renal damage.[5-9] The underlying mechanisms involved in the pathogenesis of these manifestations remain largely undefined. Animal studies have implicated the disruption of endothelium dependent and independent dilatation[10-13] as well as alteration in vascular response;[14 15] in human tissue, cyclosporin induced hypertension was associated with sympathetic neural activation.[16]

The effect of cyclosporin on the human coronary arterial system could have important clinical implications. Though the use of cyclosporin therapy has coincided with a decrease in accelerated atherosclerosis in grafted coronary arteries in transplant recipients,[17] there is some evidence that cyclosporin can have an adverse effect on the ability of the endothelium to secrete prostacyclin[18] and to enhance the production of endothelin.[19] Endothelial dysfunction could have potentially harmful effects on the vessel wall and myocardium.

In a previous study we showed that acute exposure to cyclosporin at concentrations of 100–500 ng/ml did not affect the ability of the endothelium of human coronary arteries to release the endothelium derived relaxing factor, nitric oxide, in response to substance P.[20] After short term exposure in vitro it seems that this vasodilatory mechanism is preserved. To elucidate further the influence of cyclosporin on the endothelium we examined the effect of short term and long term exposure to therapeutic and toxic doses of cyclosporin on endothelium dependent relaxation in the human coronary circulation in vitro and in vivo.

The National Heart and Lung Institute, Harefield Hospital, Harefield, Middlesex
G S O'Neil
A H Chester
S Kushwaha
M Rose
S Tadjkarimi
M H Yacoub

Correspondence to Professor Magdi H Yacoub, Thoracic and Cardiac Surgical Unit, Harefield Hospital, Harefield, Middlesex UB9 6JH.

Accepted for publication 29 April 1991

Patients and methods

IN VITRO STUDY

Epicardial coronary arteries were harvested from seven patients undergoing heart or heart-lung transplantation for reasons other than ischaemic heart disease; they were judged to be free of atheromatous plaque both macroscopically and microscopically. After dissection, they were placed in cold, modified Tyrode's solution (composition (mmol/l): NaCl 136·9, $NaHCO_3$ 11·9, KCl 2·7, NaH_2PO_4 0·4, $MgCl_2$ 2·5, $CaCl_2$ 2·5, glucose 11 1, disodium EDTA 0·04) and gassed with 95% oxygen/5% carbon dioxide for no more than eight hours.

Forty four vessel segments, 3–5 mm long, were suspended in 5 ml organ chambers between two L-shaped metal hooks, one of which was fixed and the other attached to a Grass FTO-3C strain gauge transducer connected to a Grass 79D polygraph set up to monitor and record changes in segment tension. The temperature of the bath was maintained at 37°C and the Tyrode's solution was continually gassed.

A preload of 50 mN was applied to each segment and after a stabilisation period of 40–60 minutes during which "relaxing-out" occurred and a steady baseline was reached. Potassium chloride (90 mmol/l) was applied to assess tissue viability. After washout of the potassium chloride and when a steady baseline was reached, the segments were exposed for three hours to cyclosporin (powder form donated by Sandoz). The cyclosporin was initially dissolved in methanol to give a stock solution of 0·5 mg/ml methanol; subsequent dilutions in Tyrode's solution gave final bath concentrations of 1000 and 2000 ng/ml. This dilution procedure gives a uniform solution of cyclosporin in Tyrode's solution as assessed by high performance liquid chromatography (unpublished observation). During the three hour incubation period the bath solutions were renewed once. Control incubations were performed in Tyrode's solution or methanol (at a bath concentration of methanol that was identical to that used when it was used as the diluent). A level of preconstriction, optimally 60–70% of the potassium response, was then induced with cumulative doses of the thromboxane-mimetic U46619. The relaxation profiles of the preparations were examined by comparing the responses after application of substance P (10^{-11} to 10^{-7} mol/l) with those generated by 5·3 × 10^{-6} mol/l of glyceryl trinitrate. The ability of the vessels to respond to glyceryl trinitrate was measured against the constriction produced by U46619. In a separate study, 15 segments removed from three patients undergoing re-transplantation of the heart and lung for obliterative bronchiolitis were assessed for endothelium function as described above. These patients had been shown to have angiographically normal coronary arteries and had been treated with immunosuppressive doses of cyclosporin for a mean of 22 months; in the six week period before re-transplantation blood concentrations of the cyclosporin parent compound had ranged from 43 to 258 ng/ml, and on the day before the operation concentrations were between 40 and 95 ng/ml.

IN VIVO STUDY

The effect of intracoronary substance P (1·4–24 pmol/min) and isosorbide dinitrate (2 mg for 2 minutes) infusion was also examined in 12 cardiac transplant recipients who were clinically well 1–5 years postoperatively. These substances possess only vasodilatory properties, and their use in this study was approved by the district ethics committee. The percentage changes in diameter were measured by a computerised analysis system (CAAS-Pie Data Medical). The blood concentrations of cyclosporin were simultaneously measured by a conventional radioimmunoassay targeted against the cyclosporin parent compound (INCSTAR Corporation). This assay measures total cyclosporin concentration in whole blood.

DATA ANALYSIS

For each patient in the in vitro studies some segments were used as controls while others were treated with only one concentration of cyclosporin. A mean value was obtained for each treatment within a patient, and these means were then averaged to give an overall mean (SEM) for each treatment for the group of patients as a whole. Treatments were compared by an unpaired *t* test, and significance was assigned at $p < 0·05$.

For the in vivo study the substance P and isosorbide dinitrate measurements were taken in duplicate from each patient and the means calculated. An overall mean (SEM) was then calculated for each treatment and compared by an unpaired *t* test. Linear regression analysis was applied to examine the relation between blood concentration of cyclosporin and the response to substance P and isosorbide dinitrate.

Results

In vitro study—We studied vessels removed from hearts at time of transplantation (3 hour cyclosporin incubation—acute effect) or re-transplantation (chronic effect). Substance P

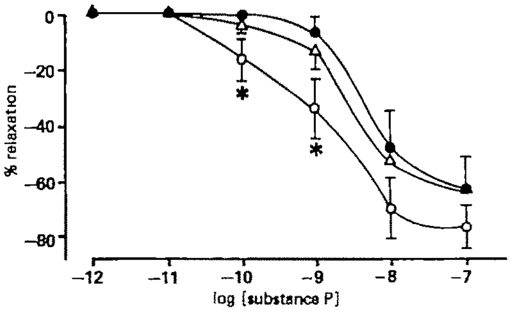


*Figure 1 Effect of cyclosporin on the relaxation induced by substance P (10^{-11}–10^{-7} mol/l) in human epicardial coronary arteries (○ = control, 16 segments from 7 patients; △ = 1000 ng/ml cyclosporin, 14 segments from 7 patients; ● = 2000 ng/ml cyclosporin, 14 segments from 7 patients). Responses are mean (SEM) of segments from seven patients, measured as percentage of relaxation in response to 5·3 × 10^{-6} mol/l glyceryl trinitrate. *$p < 0·05$.*

P, 25, 745

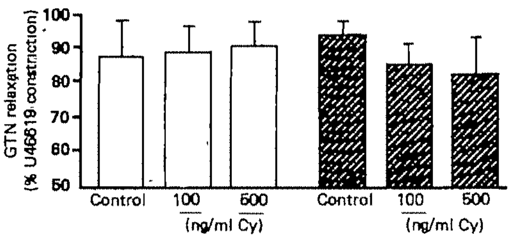


Figure 2 Effect of cyclosporin (Cy) (100–2000 ng/ml) on the relaxation induced by 5·3 × 10^{-6} mol/l glyceryl trinitrate (GTN) in human epicardial coronary arteries. Open columns: control = 12 segments from four patients; 100 ng/ml cyclosporin = 12 segments from four patients; and 500 ng/ml cyclosporin = 12 segments from four patients. Responses are means (SEM) of segments from four patients. Hatched columns: control = 16 segments from seven patients; 1000 ng/ml cyclosporin = 14 segments from seven patients; and 2000 ng/ml cyclosporin = 14 segments from seven patients. Responses are means (SEM) of segments from seven patients measured as percentage of constriction in response to U46619.

caused dose dependent relaxation in all vessel segments. In the control tissue maximum relaxation was 76·6 (7·4)% in response to 10^{-7} mol/l substance P. This was unaffected by incubation with the methanol vehicle. After incubation with 1000 ng/ml and 2000 ng/ml cyclosporin the maximum relaxations were 63·0 (11·5)% and 62·2 (11·1)% respectively. This reduction in the vasodilatory response was not statistically significant. However, at low concentrations of substance P (10^{-10} and 10^{-7} mol/l) the dilatatory response was significantly reduced ($p < 0·05$) (fig 1). Cyclosporin caused a mild but non-significant reduction ($p > 0·05$) of the relaxations produced by 5·3 × 10^{-6} mol/l glyceryl trinitrate: 1000 ng/ml, 82·3 (4·3)%, 2000 ng/ml, 82·0 (6·4)%, control, 92·8 (2·4)% (fig 2). This trend was not seen when lower concentrations of cyclosporin were used.[20]

Segments of coronary artery from the re-transplanted patients had a mean maximum response to 10^{-7} mol/l substance P of 78·0 (11·0)%, which was similar to that of the control tissue. The dose response curves were parallel for each patient although the maximum response varied (fig 3). There was no correlation between maximum response and duration of cyclosporin treatment.

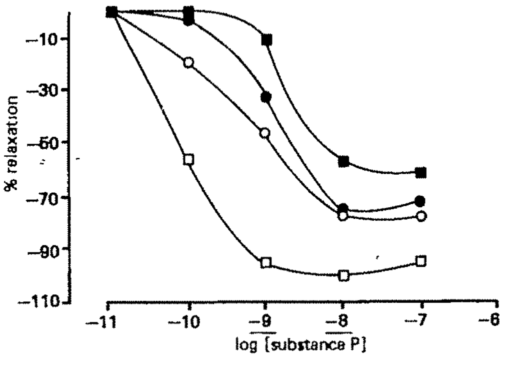


Figure 3 Relaxations to substance P (10^{-11}–10^{-7} mol/l) in 15 segments of epicardial coronary artery from three patients undergoing re-transplantation for obliterative bronchiolitis (○, mean of three patients). Patient 1 (■) 2 days cyclosporin therapy; patient 2 (●) 30 months cyclosporin therapy; patient 3 (□) 37 months cyclosporin therapy.

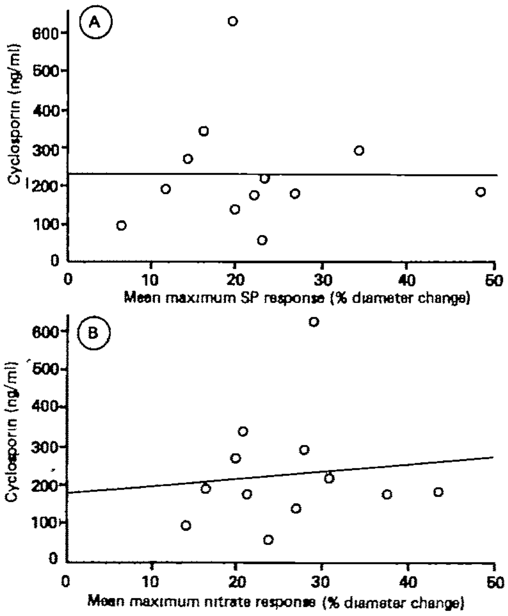


Figure 4 Correlation curves for blood cyclosporin concentrations and the in vivo responses to (A) substance P (SP) and (B) isosorbide dinitrate (ISDN) measured as percentage vessel diameter change after intracoronary SP (1 4–24 pmol/min) and ISDN (2 mg for 2 min) infusion in 12 cardiac transplant recipients assessed 1–5 years postoperatively.

In vivo study—We examined angiograms of the coronary arteries of 12 transplant recipients 1–5 years postoperatively. The mean maximum dilatations in response to substance P and isosorbide dinitrate were 22·1 (3·2)% and 26·0 (2·5)% respectively. These were significantly different from the control value ($p < 0·05$) but not significantly different from each other. There was no correlation between the blood concentration of cyclosporin and the response to either substance P or isosorbide dinitrate (fig 4A and B).

Discussion

We examined the short and long term consequences of therapeutic and toxic exposure to cyclosporin in vitro and in vivo. We showed that cyclosporin does not affect the ability of human coronary arteries to release nitric oxide in response to substance P.

Nitric oxide, released from vascular endothelium, is thought to be important in guarding against vasospasm and platelet aggregation.[21–23] The consequences of compromised nitric oxide release are now considered to be far-reaching in the human vascular system.[24–26] Loss of the protective anti-spastic and anti-aggregatory properties of nitric oxide seems to predispose toward constrictor and thrombotic events. Hypertension, renal damage, and atherosclerosis could be caused or aggravated by malfunction of the endothelium.

Nitric oxide release was reduced in animal preparations treated with cyclosporin. Specific endothelial damage was shown to be associated with the duration of cyclosporin administration. Thus after three hours[10] and five days[11] the ability of the endothelium of rat aortic rings to produce nitric oxide was affected but the complete response to endothelium independent vasodilatation with nitrates was retained. However after three weeks[13] and eight weeks[11] the smooth muscle response was reduced; so the assessment of a specific effect on the release of endothelium derived nitric oxide is difficult. We also found that in the isolated rat heart the endothelium dependent and independent responses were reduced by cyclosporin. In human tissues there seems to be a loss in the sensitivity of the relaxatory response at low concentrations of substance P; however, the nitric oxide and nitrate maximum responses are not significantly compromised. This holds true for a range of cyclosporin concentrations in both acute and chronic experiments. At high doses in vitro there was a blunting of the nitrate response which did not reach statistical significance. It is therefore possible that prolonged exposure to toxic concentrations of cyclosporin may produce smooth muscle damage.

The results obtained in coronary arteries from re-transplantation can be regarded as preliminary data from a small group of patients. They serve to confirm that the preservation of the response as measured in the in vivo study is reproducible in the isolated organ bath and that the duration of cyclosporin treatment does not correlate with inhibition of nitric oxide release.

Despite the results from the in vitro experiments, it is still possible that patients who were treated with cyclosporin for months and years have altered endothelial function. This question cannot be adequately addressed by in vitro techniques because we could only obtain a small number of arteries from patients who had been receiving cyclosporin. Therefore, the in vivo study was designed to examine the consequences of chronic exposure of the endothelium to therapeutic concentrations of cyclosporin. The mean vasodilatatory response to substance P was not significantly different from the responses obtained in normal non-transplanted patients with no coronary artery disease.[27] Chronic exposure to cyclosporin did not seem to alter endothelial function as assessed by the ability of substance P to release nitric oxide in the coronary arteries of cardiac transplant patients. We used substance P to assess endothelial function because it has a vasodilatatory action only. Previous studies of acetylcholine infusion in transplant recipients suggested endothelial dysfunction because it caused vasoconstriction.[28] However, acetylcholine produced vasoconstriction in any vessel when a high enough dose was used,[29] which makes it an unreliable agent for the examination of endothelium mediated dilatation.

Cyclosporin affected some endothelial functions; factor VIII concentration increased[30] while prostacyclin production was impaired[18]; concentrations of endothelin, the potent endothelium derived constrictor, were raised.[19] However, our study has shown that the capacity to release nitric oxide is preserved in human coronary endothelium. Cyclosporin does inhibit endothelial prostacyclin production,[18] although there has been conflicting experimental evidence on prostaglandin excretion in cyclosporin nephrotoxicity.[31] It seems that interaction of cyclosporin with endothelium derived vasodilatators has no direct role in the genesis of hypertension, renal damage, and accelerated graft atherosclerosis in the transplant recipient. It is more likely that the vasospasm and vascular damage associated with cyclosporin toxicity is caused by a combination of effects on constrictor influences (such as endothelin[19] and thromboxane[32–34]) as well as a possible direct effect of cyclosporin on smooth muscle.[14 35–37] These may be superimposed on the observed increase in sympathetic nerve activity.[16]

We conclude that the nitric oxide response remains unaffected in coronary arteries of patients exposed to cyclosporin. The mechanisms of vascular damage in patients receiving cyclosporin need further elucidation if we are to evolve rational methods of preventing this important complication.

1 Cohen DJ, Loertscher R, Rubin MF, Tilney NL, Carpenter CB, Strom TB. Cyclosporine a new immunosuppressive agent for organ transplantation. *Ann Intern Med* 1984, 101·667–82.

2 Thompson ME, Shapro AP, Johnson AM, *et al.* New onset of hypertension following cardiac transplantation a preliminary report and analysis *Transplant Proc* 1983, 15(suppl 1) 2573–7.

3 Olivari M-T, Antolick A, Ring WS Arterial hypertension in heart transplant recipients treated with triple-drug immunosuppressive therapy *J Heart Transplant* 1989; 8 34–9

4 Bennett WM, Porter GA Cyclosporin-associated hypertension. *Am J Med* 1988,85 131–3

5 Myers BD, Sibley R, Newton L, *et al.* The long-term course of cyclosporine-associated chronic nephropathy *Kidney Int* 1988,33·590–600.

6 Sweny P, Hopper J, Gross M, Varghese Z. Nephrotoxicity of cyclosporin A *Lancet* 1981,i.663–4

7 Bennett WM, Pulliam JP. Cyclosporin nephrotoxicity *Ann Intern Med* 1983,99.851–5

8 Neild GH, Reuben R, Hartley RB, Cameron JS Glomerular thrombi in renal allografts associated with cyclosporin treatment *J Clin Pathol* 1985,38.253–8.

9 Sommer BG, Innes JT, Whitehurst RM, Sharma HM, Ferguson RM Cyclosporin-associated renal arteriopathy resulting in loss of allograft function *Am J Surg* 1985, 149 156–64

10 Dinh Xuan AT, Fan TPD, Higenbottam TW, Clelland C, Wallwork J. Cyclosporin in vitro reduces endothelium-dependent relaxation to acetylcholine but does not affect relaxation to nitrovasodilators. *Transplant Proc* 1990, 22:1723–5

11 Bossaller C, Forstermann U, Hertel R, Olbricht C, Reschke V, Fleck E. Ciclosporin A inhibits endothelium-dependent vasodilation and vascular prostacyclin production. *Eur J Pharmacol* 1989;165:165–9

12 Rego A, Vargas R, Wroblewska B, Foegh ML, Ramwell PW Attenuation of vascular relaxation and cyclic GMP responses by cyclosporin A *J Pharmacol Exp Ther* 1990,252·165–70.

13 Rego A, Vargas R, Foegh ML, Ramwell PW Effect of ciclosporin A treatment on vascular reactivity of the rat thoracic aorta. *Transplant Proc* 1988,20(suppl 3)·572–7

14 Golub MS, Lustig S, Berger ME, Lee DBN Altered vascular responses in cyclosporin-treated rats *Transplantation* 1989,48 116–8

15 Rego A, Vargas R, Suarez KR, Foegh ML, Ramwell PW Mechanism of cyclosporin potentiation of vasoconstriction of the isolated rat mesenteric arterial bed role of extracellular calcium. *J Pharmacol Exp Ther* 1990, 254:799–808.

16 Scherrer U, Vissing SF, Morgan BJ, *et al* Cyclosporin-induced sympathetic activation and hypertension after heart transplantation. *N Engl J Med* 1990,323 693–9

17 Barbir M, Banner NR, Reid CJ, Thompson GR, Mitchell AG, Yacoub MH. Influence of lipid abnormalities on the development of coronary arterial disease after cardiac transplantation [abstract] *Br Heart J* 1989,61 462

18 Brown Z, Neild GH. Cyclosporin inhibits prostacyclin production by cultured human endothelial cells *Transplant Proc* 1987;19 1178–80

19 Cairns HS, Rogerson M, Fairbanks LD, Westwick J, Neild GH. Endothelin and cyclosporin nephrotoxicity. *Lancet* 1988,ii·1496–7

20 O'Neil GS, Chester AH, Rose M, Tadjkarimi S, Yacoub MH. The effect of cyclosporin A on the release of endothelium-derived relaxing factor from isolated human epicardial coronary arteries. *Transplantation* 1991; 51·735–8

21 Luscher TF *Endothelial vasoactive substances and cardiovascular disease.* Basel S Karger, 1988 1–130.

22 Radomski MW, Palmer RMJ, Moncada S. The anti-aggregatory properties of vascular endothelium· interaction between prostacyclin and nitric oxide *Br J Pharmacol* 1987;92:639–46.

23 Bassenge E, Busse R. Endothelial modulation of coronary tone *Prog Cardiovasc Dis* 1988,30 349–80.

24 Chester AH, O'Neil GS, Moncada S, Tadjkarimi S, Yacoub MH. Low basal and stimulated release of nitric oxide in atherosclerotic epicardial coronary arteries *Lancet* 1990; ii.897–900.

25 Bossaller C, Habib GB, Yamamoto H, Williams C, Wells S, Henry PD. Impaired muscarinic endothelium-dependent relaxation and cyclic guanosine 5'-monophosphate formation in atherosclerotic human coronary artery and rabbit aorta. *J Clin Invest* 1987,79:170–74

26 Luscher TF, Diedrich D, Siebenmann R, *et al.* Difference between endothelium-dependent relaxation in arterial and in venous coronary bypass grafts *N Engl J Med* 1988; 319 462–7.

27 Crossman DC, Larkin SW, Fuller RW, Davies GJ, Maseri A. Substance P dilates epicardial coronary arteries and increases blood flow in humans *Circulation* 1989,80 475–84.

28 Nellessen U, Lee TC, Fischell TA, *et al.* Effects of acetylcholine on epicardial coronary arteries after cardiac transplantation without evidence of fixed graft recording *Am J Cardiol* 1988;62:1093–7

29 Newman CM, Hackett DR, Fryer M, El-Tamimi HM, Davies GJ, Maseri A. Dual effects of acetylcholine on angiographically normal human coronary arteries in vivo. *Circulation* 1987;76(suppl IV) 238–45.

30 Brown Z, Neild GH, Willoughby JJ, *et al* Increased factor VIII as an index of vascular injury in cyclosporin nephrotoxicity. *Transplantation* 1986,42 150–3

31 Neild GH Cyclosporin nephrotoxicity. *Seminars in Thoracic and Cardiovascular Surgery* 1990;2:198–203.

32 Kawaguchi A, Goldman MH, Shapiro R, *et al.* Increase in urinary thromboxane B2 in rats caused by cyclosporin. *Transplantation* 1985,40:214–6.

33 Petric R, Freeman D, Wallace C, McDonald J, Stiller C, Keown P Modulation of experimental cyclosporin nephrotoxicity by inhibition of thromboxane synthesis. *Transplantation* 1990;50.558–63.

34 Perico N, Benigni A, Zoja C, *et al* Functional significance of exaggerated renal thromboxane A2 synthesis induced by cyclosporin A. *Am J Physiol* 1986;251.F581–7.

35 Xue H, Bukoski RD, McCarron DA, Bennett WH Induction of contraction in isolated rat aorta by cyclosporine. *Transplantation* 1987;43:715–8.

36 Pfeilschifter J, Ruegg UT Cyclosporin A augments angiotensin II-stimulated rise in intracellular free calcium in vascular smooth muscle cells. *Biochem J* 1987,248.883–7.

37 Meyer-Lehnert H, Schrier RW. Cyclosporin A enhances vasopressin-induced Ca^{2+} mobilization and contraction in mesangial cells. *Kidney Int* 1988,34:89–97.

Br Heart J 1991;66 217–220

Genesis of Still's murmurs: a controlled Doppler echocardiographic study

H M Gardiner, H S Joffe

Abstract

Objective—**The origin of innocent systolic murmurs is uncertain. This study was designed to evaluate the relative contribution in the same subjects of the main factors implicated in the genesis of vibratory innocent systolic murmurs—that is, the presence of left ventricular bands and increased left ventricular flow indices—and to examine evidence for turbulence in relation to these findings.**

Patients—**40 children with innocent systolic murmurs and 40 paired controls without murmurs were matched for age and body surface area.**

Design—**These subjects were examined prospectively by cross sectional echocardiography with pulsed and continuous wave Doppler and colour flow mapping.**

Setting—**A tertiary referral centre for paediatric cardiology.**

Results—**Left ventricular bands were significantly more prevalent in patients with innocent murmurs (70%) than in controls (48%) but only if apical bands were included ($p = 0\cdot039$). Cases had significantly higher aortic peak flow velocities ($p < 0\cdot001$), flow integrals ($p = 0\cdot001$), and stroke volumes ($p = 0\cdot014$), and significantly lower heart rates ($p = 0\cdot033$) than controls. There were no significant differences between cases and controls in mean aortic diameter, cardiac output, or ejection fraction. There was no evidence of turbulence in the left ventricle or outflow tract in any individual but curvilinear periodic vibrations and audible "whoops" were detected in the left ventricle by pulsed wave Doppler echocardiography. These were significantly more common in cases than controls ($p < 0\cdot01$) but were not related to the presence of bands.**

Conclusions—**Innocent systolic murmurs were unrelated to aortic size but they were strongly associated with higher aortic flow volume and velocity, with relative bradycardia, and with evidence of vibratory phenomena in the left ventricle. The role of left ventricular bands remains uncertain.**

Royal Hospital for Sick Children, Bristol
H M Gardiner
H S Joffe

Correspondence to
Dr H S Joffe, Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ.

Accepted for publication
14 May 1991

Innocent systolic murmurs are audible in up to 70% of school-children.[1] They are characterised by their musical sound and, as their name suggests, are benign and cause no symptoms. They usually disappear during adolescence. The origin of a musical systolic murmur is still a matter for debate: some studies suggest that it is caused by the vibration of intracardiac structures such as valves in hearts with structural abnormalities[2–4]; others suggest that vibrations of left ventricular bands or turbulent flow about these structures cause the innocent systolic murmur.[5 6]

Left ventricular flow characteristics have also been investigated as a possible cause of the murmur. Schwarz *et al* reported that the peak velocities in the ascending and descending aorta were significantly greater in children with innocent murmurs and ascribed this to a narrower aortic diameter in this group compared with children without murmurs.[7] These findings were confirmed by Sholler and colleagues[8] but not by Van Oort *et al* who found no difference in the peak velocity, acceleration, or spectral width of the aortic flow signal between children with innocent murmurs and children without.[9] There is currently no consensus on the origin of the musical murmur in structurally normal hearts.

This study was designed to determine the prevalence of bands, the presence of turbulence about the bands and in the left ventricular outflow tract, and left ventricular flow characteristics and systolic function in children with innocent murmurs and without.

Patients and methods

We studied 40 symptom free children (aged 5 months to 13 years) who had been referred to the Bristol Children's Hospital for evaluation of murmurs and were found to have the characteristic musical and vibratory bruit of the Still's innocent murmur. The control group consisted of 40 children without murmurs. They were inpatients who were fully recovered after a transient acute illness (40%) or children whose parents had responded to a written request for participants for this study (60%). Each study child was matched for age and body surface area with a control child (table 1).

The children were studied in the supine or left decubitus position by the Hewlett Packard 77500C machine with a 5 or 3·5 MHz transducer. A concurrent electrocardiograph recording was taken to time events and obtain heart rates. The heart was examined in standard planes by cross sectional real time ultrasound and pulsed and continuous wave Doppler.

Table 1 Clinical and flow data (mean [SD]) of cases and controls

Data	*Cases* *(n = 40)*	*Controls* *(n = 40)*	*t test*	*p value*
Age (month)	60 (39)	63 (40)	1·14	NS
BSA (m^2)	0·76 (0·26)	0·77 (0·26)	0·46	NS
Aortic data:				
Ao diam (cm)	1·41 (0·24)	1·44 (0·29)	0·72	NS
Acceln (m/s^2)	23·38 (4·96)	21·70 (5·58)	1·57	NS
Peak flow (m/s)	1·62 (0·18)	1·41 (0·19)	5·05	<0·001
Flow integral	26·59 (4·45)	21·20 (3·39)	6·05	<0·001
EF	0·81 (0·07)	0·80 (0·06)	0·28	NS
Stroke vol (ml)	44·12 (18·18)	38·07 (18·39)	2·58	0·014
Heart rate (beats/min)	94·8 (23·5)	101·8 (22·0)	2·21	0·033
CO (l/min)	3·96 (1·38)	3·62 (1·27)	1·20	NS
Pulmonary data	(n = 28)	(n = 28)		
Peak flow (m/s)	82·92 (12·86)	86·37 (13·60)	−0·64	NS
Flow integral	14·46 (3·19)	15·65 (2·25)	−1·22	NS

BSA, body surface area; Ao diam, aortic diameter; Acceln, acceleration; EF, ejection fraction; Stroke vol, stroke volume; CO, cardiac output.

PREVALENCE OF LEFT VENTRICULAR BANDS

The number and site of any bands in the left ventricle was noted. Off axis views were sometimes required to determine the presence of bands and to distinguish them from left ventricular trabeculations.[10]

ASSESSMENT OF TURBULENT FLOW

The pulsed wave Doppler sample was placed at three sites along the apical aspect and at three similar sites along the basal aspect of the band and the flow pattern in each location was recorded. Similar recordings were made in the children without bands, by sampling the four sites nearest to the ventricular walls to enable the wave patterns produced about the bands to be compared with those produced by the trabeculae along the ventricular walls. Pulsed wave Doppler recordings were also made approximately 1 cm proximal to the aortic valve in the left ventricular outflow tract. Colour flow imaging of the left atrium, left ventricle, and left ventricular outflow tract was recorded from the parasternal and apical long axis views. A high parasternal long axis view was used to assess flow patterns in the aortic root and ascending aorta and this or a short axis view was used to record flow in the right ventricular outflow tract and pulmonary artery.

LEFT VENTRICULAR FUNCTION

Continuous wave Doppler recordings[11] were made from the suprasternal notch[12 13] and the maximum velocity (peak flow), time to peak (acceleration), and flow integral in the ascending aorta were measured in systole (the mean of six measurements for each index was recorded). We used a non-steerable off axis continuous wave pencil probe because this facilitated the acquisition of higher quality and more uniform traces in children of various sizes than the larger pulsed wave probe.[14] Because continuous wave Doppler measures velocity within the aortic ring or the narrowest portion of the left ventricular outflow tract,[15] the diameter of the aortic root was calculated from a mean of six measurements taken at the origin of the cusps during maximal separation of the aortic valve leaflets.

We used the Hewlett Packard software package to calculate the stroke volume from the flow integral and cross sectional area of the aorta and the cardiac output from the stroke volume and the heart rate. For the ejection fraction the internal diameter of the left ventricle was measured at the level of the tips of the mitral valve—firstly at the end of diastole (Ed) just after mitral valve closure and then at the end of systole (Es) just after aortic valve closure but before mitral valve opening. The ejection fraction was calculated as Ed − Es/Ed.

RIGHT VENTRICULAR FUNCTION

Pulmonary peak velocities and flow integrals were recorded by pulsed wave Doppler from a high parasternal long or short axis view in all cases where adequate traces were obtained (28 pairs of children). Because of poor reproducibility of pulmonary artery diameters,[16] derived estimates of right ventricular stroke volume and cardiac output were not obtained.

DATA COLLECTION

The examinations were recorded on videotape for later batch analysis by the Hewlett Packard software package. Data analysis was performed without knowledge of the status of the child (case or control).

STATISTICAL ANALYSIS

McNemar, χ^2, and Student's *t* test were used to analyse paired non-parametric data, non-paired non-parametric data, and paired parametric data respectively. A p value of $<0·05$ was regarded as significant.

Results

PREVALENCE OF LEFT VENTRICULAR BANDS

Twenty eight cases (70%) and 19 controls (48%) had bands in the left ventricle. Several subjects had more than one band and table 2 shows the number and location of bands. Bands of all types were significantly more common in children with murmurs than in those without (McNemar's test, p = 0·0389) and the relative risk of a child with an innocent murmur having a band in this study was calculated as 2·8:1 (95% CI 1·2 to 10·1). However, if the four children with apical bands only were regarded as having no bands the difference between the two groups was not significant. Unlike the findings of Darazs *et al*, there was no significant difference in the location of the bands between the two groups in this study.[6]

Table 2 Number and location of left ventricular bands

	Number of children		Number of bands	
Site of band	*Cases*	*Controls*	*Cases*	*Controls*
LVOT	2	2	2	2
MC	13	13	15	15
A/S	4	0	6	0
LVOT+MC	1	1	3	2
LVOT+A/S	5	0	12	0
MC+A/S	2	3	6	8
LVOT+MC+A/S	1	0	3	0
Total	28	19	47	27

LVOT, left ventricular outflow tract; MC, mid-cavity; A, apex; S, septum.

ASSESSMENT OF TURBULENCE

By pulsed wave Doppler

Unusual Doppler patterns within the left ventricle were detected in 25 children (figure). These took the form of curvilinear harmonic vibrations during systole, usually in the opposite direction to the flow signal, and they were associated with audible simultaneous "whoops" on the microphone. These patterns were seen more often in cases than controls (18/40 *v* 7/40; $\chi^2 = 7\cdot040$, $p < 0\cdot01$). The harmonic vibrations were seen about the bands in 19 (38%) of the 47 children with bands and in seven (21%) of the 33 children without bands—along the septum in two cases, in the left ventricular outflow tract in a further two cases, and at both sites in three. There was no significant difference in the frequency of curvilinear systolic vibrations between the children with bands and those without ($\chi^2 = 3\cdot262$, p = NS) and there was no relation between these harmonic flow patterns and the position or orientation of the bands.

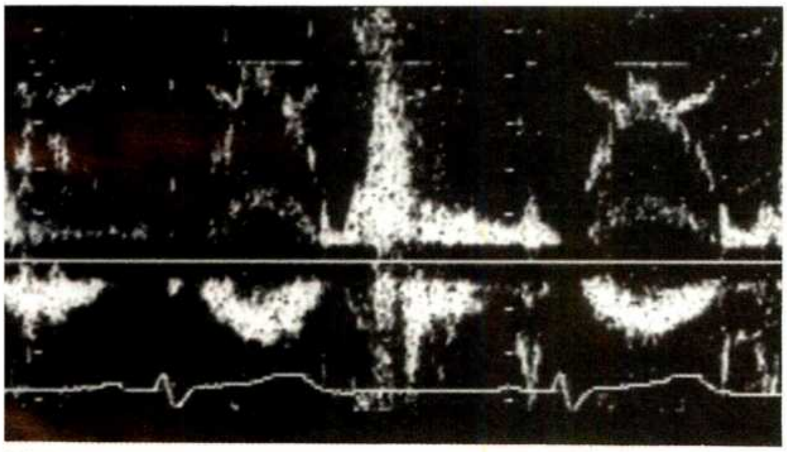
The 28 children with bands but no detectable evidence of turbulence included 15 who also had murmurs.

By colour flow mapping

We were unable to detect colour flow evidence of turbulent flow about the bands, along the ventricular walls, or in the left ventricular outflow tract in any of the cases or controls.

LEFT VENTRICULAR FLOW CHARACTERISTICS

Table 1 shows all the measurements (mean (SD)) and paired *t* test analyses. There was no significant difference in the diameter of the aortic root between the cases and controls nor in the rate of acceleration of flow through the valve. The ejection fraction did not differ in the two groups of children; but the mean peak flow, flow integral, and stroke volume were significantly greater in the cases than the controls. However, the cardiac output of the cases was similar to that of the controls, mainly owing to the significantly lower heart rate in the cases.



Pulsed wave Doppler as seen adjacent to trabeculae or about a left ventricular band, howing curvilinear periodic vibrations during systole in the opposite direction to the egative flow signal.

RIGHT VENTRICULAR FLOW CHARACTERISTICS

There was no significant difference in the mean pulmonary peak flow or flow integrals between the cases and the controls.

Discussion

Van Oort *et al* stated that innocent murmurs could not commonly be produced by left ventricular bands because bands were much less prevalent (0·8% paediatric patients) than innocent murmurs.[9] However, the reported prevalence of left ventricular bands varied widely and often depended on whether the study was prospective or retrospective because off axis views were often essential to detect their presence.[10 17 18] The prevalence of bands in this study (70% cases and 48% controls) was less than that reported in Darazs *et al*'s prospective study (92% and 64% respectively), but they found a prevalence of only 22% in their first retrospective report.[6] Keren *et al* confirmed the reliability of echocardiographic diagnosis of left ventricular bands in patients undergoing cardiac transplantation but cautioned that apical trabeculations could be misinterpreted as bands.[18] In this study, when the McNemar analysis for paired data was repeated and any child with apical bands only (n = 4) was classified as having no bands, the prevalence of left ventricular bands in cases and controls was not significantly different.

It is widely accepted that innocent murmurs are less prevalent in older children and Harpin *et al* reported a temporal association between the disappearance of the left ventricular band and the murmur in one patient who was followed longitudinally.[5] There are, however, no large longitudinal studies to provide supporting data for this observation and, indeed, a cross sectional study by Boyd *et al* found that the prevalence of left ventricular bands at necropsy was similar in each decade of life (68%).[19]

We saw no turbulence about the bands during colour flow mapping, but we detected systolic curvilinear harmonic patterns in the left ventricle by pulsed wave Doppler, which were similar to those detected by Pennestri *et al* using continuous wave Doppler in hearts with structural abnormalities.[2] They showed that murmurs can be produced by the vibration of intracardiac structures in the absence of turbulent flow. In our study these periodic vibrations and the audible systolic "whoops" were not confined to sites about the band, however, but could be clearly shown along the left ventricular walls. Although the relation of bands to murmurs was tenuous (see above), "whoops" were significantly more common in children with murmurs than in those without, suggesting that these appearances may be produced by vibration of the trabeculae lining the ventricular walls.

While the pulmonary peak flow and flow integrals did not differ significantly between cases and controls, the mean aortic peak flow, flow integral, and stroke volume were significantly greater in children with murmurs than in those without. These results support the observations of Schwarz *et al* that higher flow indices from the left side of the heart are seen in children with murmurs: but we could not confirm their finding that this is owing to the children with murmurs having smaller aortic diameters.[7] It is unlikely that measurement of the aortic diameter at different levels (in the ascending aorta in their study and at the aortic valve in ours) accounted for this disparity. In contrast to the closely matched pairs of cases and controls in our study, the two groups in Schwarz *et al*'s series were very different in terms of age and body surface area, though the difference in aortic diameter remained significant when corrected for body surface area.

Our study showed no difference in acceleration through the aortic valve between the cases and controls, nor did it seem that increased force of contraction was responsible for the murmur because the ejection fractions were similar in both groups. However, children with systolic murmurs had significantly lower heart rates than those without murmurs. Nearly all patients with very slow heart rates due to junctional bradycardia or complete heart block have a systolic murmur. It is possible that the prolonged diastolic filling of the left ventricle associated with a slower heart rate in the face of an unchanged ejection fraction and cardiac output, results in a higher stroke volume and aortic flow velocity and augments the intensity of the murmur. This explanation accords with the frequently observed finding that the innocent murmur becomes louder in the supine position—that is, when the heart rate naturally slows.

This study shows that there is a relation between vibratory phenomena within the left ventricle and the Still's vibratory murmur but the exact mechanism for its production requires further investigation and other factors may be implicated. The murmur seems to be augmented by increased flow volume and velocity and relative bradycardia; the role of left ventricular bands remains uncertain.

We thank our colleagues Dr S C Jordan and Dr R P Martin for referring suitable cases to us for this study and to Mrs J Evans and Mrs K Waters for their statistical advice.

1 McLaren MJ, Lachman AS, Pocock WA, Barlow JB. Innocent murmurs and third heart sounds in Black schoolchildren. *Br Heart J* 1980;**43**:67–73.

2 Pennestri F, Boccardi L, Minardi G, Di Segni M, Pucci E, Biasucci LM, *et al*. Doppler study of precordial musical murmurs. *Am J Cardiol* 1989;**63**:1390–4.

3 Sheikh MU, Lee WR, Mills RJ, Dais K. Musical murmurs: clinical implications, long-term prognosis, and echophonocardiographic features. *Am Heart J* 1984;**108**: 377–86.

4 Stein PD, Sabbah HN, Milligan DJ, Lakier JB. Mechanism of a musical systolic murmur caused by a degenerated porcine bioprosthetic valve. *Am J Cardiol* 1982;**49**: 1874–82.

5 Harpin VA, Ostman Smith I. The association of left ventricular tissue bands with vibratory innocent murmurs. Proceedings of the 59th annual meeting of the British Paediatric Association. *Arch Dis Child* 1987; **62**:645–52.

6 Darazs B, Hesdorffer CS, Butterworth AM, Ziady F. The possible etiology of the vibratory systolic murmur. *Clin Cardiol* 1987;**10**:341–6.

7 Schwarz ML, Goldberg SJ, Wilson N, Allen HD, Marx GR. Relation of Still's murmur, small aortic diameter and high aortic velocity. *Am J Cardiol* 1986;**57**:1344–8.

8 Sholler GF, Celermajer JM, Wright CM. Doppler echocardiographic assessment of cardiac output in normal children with and without innocent precordial murmurs. *Am J Cardiol* 1987;**59**:487–8.

9 Van Oort A, Van Dam I, Heringa A, Alsters J, Hopman J, Daniels O. The vibratory innocent heart murmur studied by echo-doppler. *Acta Paediatr Scand* 1986;suppl 329: 103–7.

10 Brenner JI, Baker K, Ringel RE, Berman MA. Echocardiographic evidence of left ventricular bands in infants and children. *J Am Coll Cardiol* 1984;**3**:1515–20.

11 Chandraratua PA, Nanna M, McKay C, Nimalasuriaya A, Swinney R, Elkayam U, *et al*. Determination of cardiac output by transcutaneous continuous wave ultrasonic Doppler computer. *Am J Cardiol* 1984;**53**:234–7.

12 Marx GR, Goldberg SJ, Allen HD. Two methods for measurement of ascending aortic diameter by 2D echocardiography as compared with cineangiography. *Am Heart J* 1986;**112**:172–3.

13 Hudson I, Houston A, Aitchison T, Holland B, Turner T. Reproducibility of measurements of cardiac output in newborn infants by Doppler ultrasound. *Arch Dis Child* 1990;**65**:15–19.

14 Goldberg SJ, Sahn DJ, Allen HD, Valdez-Cruz LM, Hoenecke H, Carnahan Y. Evaluation of pulmonary and systemic blood flow by two-dimensional Doppler echocardiography using fast Fourier transform spectral analysis. *Am J Cardiol* 1982;**50**:1394–1400.

15 Loeber CP, Goldberg SJ, Allen HD. Doppler echocardiographic comparison of flows distal to the four cardiac valves. *J Am Coll Cardiol* 1984;**4**:268–72.

16 Dickenson DF, Goldberg SJ, Wilson N. A comparison of information gained by cardiac catheterisation and ultrasound examination in pediatric patients with congenital heart disease. *Int J Cardiol* 1985;**9**:275–85.

17 Nishimura T, Kondo M, Shimada T, Shimono Y, Mukohyama N. Echocardiographic features of false tendons: with special reference to phonocardiographic significance. *J Cardiogr* 1981;**11**:253–63.

18 Keren A, Billingham ME, Popp RL. Echocardiographic recognition and implications of ventricular hypertrophic trabeculations and aberrant bands. *Circulation* 1984; **70**:836–42.

19 Boyd MT, Seward JB, Tajik AJ, Edwards WD. Frequency and location of prominent left ventricular trabeculations at autopsy in 474 normal human hearts: implications for evaluation of mural thrombi by two dimensional echocardiography. *J Am Coll Cardiol* 1987;**9**:323–6.

Quinton : when you're looking for the best in Cardiology equipment.

The Q-Cath's new approach to signal conditioning minimizes baseline drift and improves signal fidelity. All signals are transmitted digitally to ensure high noise immunity.

For many years Quinton has been dedicated to producing professional cardiology products.

From the Q-Cath, a sophisticated catheter lab, to a single ECG electrode, the Quinton name has become synonymous with quality.

The Q5000's signal processing system uses Absolute Spatial Vector Velocity (ASVV). This accurately recomputes the J-point continually during a stress test.

Quinton stress-test products include a complete range of rugged treadmills and controllers.

These range from the easy-to-use Q3000 – ideal for clinics and smaller hospitals, to the sophisticated Q5000 with touch-screen control and integral hard-disk data storage.

The Q750's high resolution thermal-array chart-recorder uses sophisticated interpretive software to print a range of formatted reports.

The Q412 non-invasive blood pressure monitor can be used with any stress-test system and measures blood pressure simply and accurately – even during stress-tests.

The new Q412 uses the accurate Pulse Korotkoff-sound Threshold (PKT) method of measurement, which synchronizes with the patient's ECG to give extremely accurate blood pressures.

The Quinton range of ECG machines include versions with integral Liquid Crystal Display, interpretive analysis and data storage.

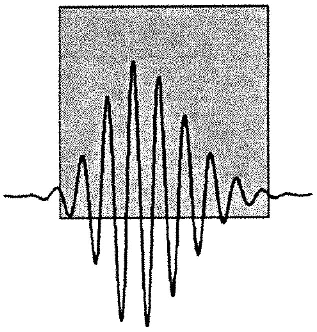
However many ECG's you do there's a model to suit your Department.

The new Q950/Q960 Holter systems feature manual or fully automatic analysis of ECG's, making it easy for busy staff to analyse and report on many more patients per day.

Try the Quinton products for yourself and we guarantee you won't be disappointed.

S&W Vickers

Ruxley Corner, Sidcup, Kent, DA14 5BL Tel. 081- 309 0433 Fax 081- 309 0919
32 Kerse Road, Stirling, FK7 7TA Tel. 0786 51602 Fax 0786 51603
4 Balmoral Business Park, Boucher Crescent, Belfast, BT12 6HU Tel. 0232 669266



Comparative Evaluation
of
Imaging and Doppler Ultrasound Systems for Examination of the Heart

A report of a technical and clinical evaluation of six ultrasound systems:

Acuson 128	Hewlett Packard Sonos 1000
Aloka SSD 870	Toshiba SSH 160
ATL Ultramark 9 (Phase 2)	Vingmed CFM 750

(£25 - free to N.H.S.)

Part of a programme sponsored by the Advisory Panel on Evaluation of Medical and Scientific Equipment and Health Service Supplies and funded by the Chief Scientist Organisation
Scottish Office Home and Health Department

-------✂--

Please send me a copy of the report on a Comparative Evaluation of Imaging and Doppler Ultrasound Systems for Examination of the Heart ☐
(Non N.H.S. please enclose a cheque to the value of £25 in favour of "Common Services Agency")

Please put my name on the mailing list for future Ultrasound Equipment Evaluation reports ☐

Name ....
Title ....
Address ....
....
....
....

Send form to: A. Watt, Common Services Agency, Supplies Division, Trinity Park House, South Trinity Road, EDINBURGH EH5 3SH (☎ 031 552 6255 ext 2077)

BHJ

Br Heart J 1991;66:221–4

Moderate hypothermia in the management of resistant automatic tachycardias in children

Seshadri Balaji, Ian Sullivan, John Deanfield, Ian James

Cardiothoracic Unit, Hospital for Sick Children, Great Ormond Street, London
S Balaji
I Sullivan
J Deanfield
I James

Correspondence to
Dr Ian Sullivan,
Hospital for Sick Children,
Great Ormond Street,
London WC1N 3JH.

Accepted for publication
29 April 1991

Abstract

***Background*—Automatic focus tachycardias are often resistant to electrical and pharmacological treatment. Moderate systemic hypothermia (32–34°C) may reduce the tachycardia rate in children with His bundle tachycardia after cardiac surgery.**

***Methods*—The case notes of seven children with automatic focus tachycardias treated with hypothermia were reviewed. Six had His bundle tachycardia after cardiac surgery and one had ectopic atrial tachycardia; all had signs of low cardiac output.**

***Results*—Hypothermia led to a reduction in heart rate in all patients (from 211 (28) (mean (SD)) to 146 (5) beats/minute, $p < 0.001$), with rises in systolic blood pressure (from 74 (14) mm Hg to 97 (10) mm Hg, $p < 0.01$) and hourly urine output (from 0·5 (0·4) ml/kg to 4·6 (2·8) ml/kg, $p < 0.02$). No direct adverse effects were noted. The arrhythmia did not resolve in three children, who died (two with His bundle tachycardia after Fontan procedures and one with ectopic atrial tachycardia); the other four regained sinus rhythm which was maintained at follow up of 3–13 (mean 9) months.**

***Conclusions*—Moderate systemic hypothermia led to slowing of the arrhythmia rate and an improvement in cardiac output in patients with resistant automatic focus tachycardias. It can be used to improve the haemodynamic condition while other measures of arrhythmia control are being pursued or until spontaneous recovery of normal rhythm.**

Table 1 Clinical details

Patient No	*Age*	*Sex*	*Diagnosis*	*Procedure*	*Arrhy*	*Conventional treatment*
1	4 days	M	TGA, VSD	BAS	EAT	Ad, Am, DCS, Dig, Fl, Pr
2	7 mnth	M	VSD	Repair	HBT	—
3	11 mnth	M	TOF	Repair	HBT	Am, Fl
4	12 mnth	F	TOF	Repair	HBT	—
5	22 mnth	M	TOF, MBTS	Repair	HBT	Overdrive pacing
6	2 yr	M	TA, PS, MBTS	F(APC)	HBT	
7	4 yr	M	DILV, PS, MBTS	F(TCPC)	HBT	Am, Dig, Fl

Ad, adenosine; Am, amiodarone; APC, atriopulmonary connection; BAS, balloon atrial septostomy; DCS, direct current shock; Dig, digoxin; DILV, double inlet left ventricle; EAT, ectopic atrial tachycardia; F, Fontan procedure; Fl, flecainide; HBT, His bundle tachycardia; MBTS, modified Blalock Taussig shunt; Pr, propranolol; PS, pulmonary stenosis; TA, tricuspid atresia; TOF, tetralogy of Fallot; TGA, transposition of the great arteries; TCPC, total cavopulmonary connection; VSD, ventricular septal defect.

In children with congenital heart disease automatic tachycardia is often resistant to electrical and pharmacological treatment[1] and may lead to fatal haemodynamic deterioration.[1,2] Some automatic tachycardias, notably His bundle tachycardia after cardiac surgery, are self-limiting.[3] Any measures that might improve the haemodynamic state could be useful in the management of the patient while other means of controlling the tachycardia are being pursued or while spontaneous recovery is awaited.

Hypothermia reduced the automaticity of all the cardiac pacemaker tissues[4] and it was beneficial in the management of His bundle tachycardia after cardiac surgery.[5,6] We report the effect of moderate hypothermia (32°C to 34°C) in seven children with resistant automatic tachycardias and congenital heart disease.

Patients and methods

PATIENTS

Between November 1988 and July 1990 we used moderate hypothermia to treat seven children with resistant tachycardia. Table 1 shows their clinical details.

A 4 day old boy who had undergone balloon atrial septostomy on the third day of life for transposition of the great arteries with a ventricular septal defect developed incessant ectopic atrial tachycardia with a rate of 200–220 beats per minute. Administration of adenosine produced brief atrioventricular block (fig 1). Drug treatment was attempted, initially with digoxin, then with digoxin and propranolol, subsequently with flecainide, and lastly with amiodarone, but the tachycardia rate fell by less than 30 beats per minute. At the age of 20 days he underwent electrophysiological study and a high right atrial focus for the tachycardia was identified. Hypothermia was started when his haemodynamic state deteriorated after an unsuccessful attempt at surgical cryoablation of the focus of the arrhythmia.

The other six patients developed His bundle tachycardia 2–48 hours after cardiac surgery. Antiarrhythmic drug treatment was started in the first two patients (amiodarone and flecainide respectively in numbers 3 and 7 (table 1)) but it had no effect on the heart rate or the rhythm. Amiodarone was continued as an infusion in patient 3 and flecainide in patient 7 during the period of hypothermia.

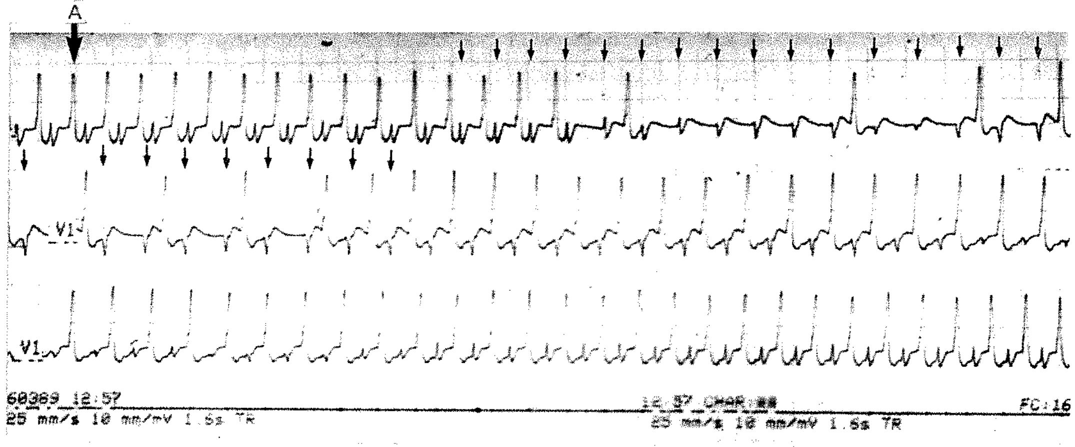


Figure 1 Continuous electrocardiographic recording (surface lead V1) in a child with ectopic atrial tachycardia (patient 1). Adenosine was given at point A (arrow) and caused transient atrioventricular nodal block which unmasked the atrial tachycardia (small arrows).

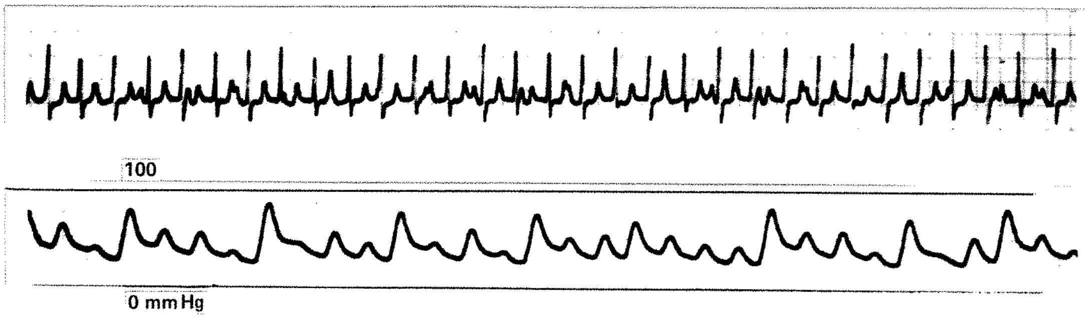


Figure 2 Electrocardiogram (lead II) and blood pressure tracing of a patient with His bundle tachycardia showing a narrow QRS complex tachycardia with atrioventricular dissociation and considerable beat to beat variability of blood pressure.

Patient 7 was also treated with digoxin throughout his postoperative course.

After this early experience hypothermia was used as the initial treatment in patients developing His bundle tachycardia after cardiac surgery. However, overdrive pacing was attempted, without success, in one patient (patient 5) before hypothermia was induced.

METHODS

Arrhythmia diagnosis

The diagnosis of His bundle tachycardia was based on the presence of a regular tachycardia with a QRS complex similar to that in sinus rhythm. Each patient had atrioventricular dissociation and a ventricular rate in excess of the atrial rate (fig 2). Atrial electrograms recorded via the atrial pacing lead inserted at the time of surgery confirmed the diagnosis (fig 3). The evidence of beat to beat variability in the arterial pressure trace despite the presence of a regular ventricular rhythm further supported the diagnosis of atrioventricular dissociation (fig 2).

Ectopic atrial tachycardia was diagnosed in a neonate with 1:1 atrioventricular relation and a heart rate which was consistently 200–220 beats per minute. The highest heart rate (mean (SD)) in normal neonates in sinus rhythm is 179 (19) beats/minute.[7] When adenosine induced a transient atrioventricular block the atrial tachycardia was unmasked (fig 1). The diagnosis was confirmed by invasive electrophysiological study.

Hypothermia

Surface cooling was achieved by placing ice packs around the head and by gastric irrigation with cold water. If this proved inadequate a heat exchanging blanket was placed under the patient to achieve the desired core temperature. The rectal temperature was used as the reference value in all patients. All patients were sedated, paralysed, and on ventilatory support during the period of hypothermia.

Patients were cooled to a temperature of 32–34°C until the heart rate fell to 150 beats per minute or less. Once started, cooling was maintained for at least 36 hours. Cooling was stopped when the patient was judged to have been stable for at least 24 hours (on the basis of continuous measurement of blood pressure and urine output and intermittent arterial blood gas analysis). Resolution of the arrhythmia was not a criterion for rewarming.

Results

ECTOPIC ATRIAL TACHYCARDIA

In the one neonate with this arrhythmia the heart rate fell from 220 to 150 beats per minute

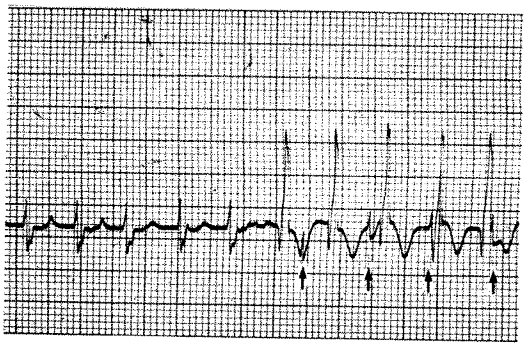


Figure 3 Electrogram recorded from an atrial epicardial pacing wire (right half of the picture) showing His bundle tachycardia in a patient in whom the standard electrocardiogram (lead II, left) was not diagnostic. The arrows indicate atrial depolarisation.

Table 2 Data on hypothermia treatment

Patient No	*Interval* (h)*	*HR during arrhy (beats/min)*	*Central T° during arrhy (°C)*	*Central T° cooled (°C)*	*HR when cooled (beats/min)*	*Duration cooled*	*Outcome*
1	24	220	37	32	150	4 days	Died†
2	2	250	39 5	34	150	5 days	SR
3	18	230	38	34	150	38 h	SR
4	2	220	37 5	33	140	67 h	SR
5	48	210	37	34	140	36 h	SR
6	48	170	39	34	150	48 h	Died
7	2	180	40	33	140	48 h	Died

*Between procedures and onset of arrhythmia.
†Died at surgery (Senning procedure).
HR, heart rate, SR, sinus rhythm, T°, temperature.

with apparent improvement in cardiac output when cooling to a temperature of 32°C was started. Systolic blood pressure improved from 60 to 70 mm Hg and hourly urine output, which had been 0·2 ml/kg for the four hours before hypothermia, improved to 1·6 ml/kg for the next four hours. He was stable for the next four days. When he was allowed to become normothermic, however, the ectopic atrial tachycardia rate increased to 200 beats/minute and he remained dependent on assisted ventilation and peritoneal dialysis. Eventually, a Senning procedure with closure of ventricular septal defect was undertaken on day 26 in the hope that the extensive atrial surgery might ablate the focus for the tachycardia. Unfortunately he could not be weaned from cardiopulmonary bypass.

HIS BUNDLE TACHYCARDIA

Six patients had His bundle tachycardia after cardiac surgery. Four of these had surgery in the region of the atrioventricular bundle: repair of tetralogy of Fallot in three and closure of a perimembraneous inlet' ventricular septal defect in one. The other two patients had Fontan operations—one an atriopulmonary connection and the other a total cavopulmonary connection.

Conventional antiarrhythmic drug treatment was the initial treatment in two patients (table 1) but it did not restore sinus rhythm or reduce the heart rate to below 180 beats per minute (table 2). Treatment with antiarrhythmic drugs (amiodarone in one and digoxin and flecainide in another) was continued in two patients. Surface cooling reduced the heart rate and improved indirect measures of cardiac output in all cases. Systolic blood pressure improved from 77 (14) mm Hg (mean (SD)) at the start of cooling to 97 (10) mm Hg ($p < 0·01$) when the target core temperature was reached (fig 4). Hourly urine output improved from 0·5 (0·4) ml/kg for the four hours before hypothermia to 4·6 (2·8) for the first four hours after the start of hypothermia ($p < 0·02$) (fig 4). Figure 5 shows the effect of starting hypothermia on the heart rate and urine output in patient 3.

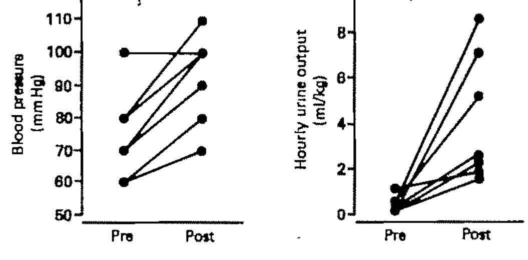


Figure 4 Effect of hypothermia on systolic blood pressure and urine output in all seven patients. See text for details of measurement.

Two children regained sinus rhythm while they were still hypothermic (after four hours in patient 5 and after 66 hours in patient 4). Hypothermia was continued at 34°C in patient 5 for a further 32 hours as a precaution against the recurrence of the tachycardia, while patient 4 was rewarmed one hour after sinus rhythm was regained. Two other children (patients 2 and 3) regained sinus rhythm 40 and 84 hours respectively after rewarming. The two children who had undergone Fontan procedures (patients 6 and 7) did not regain sinus rhythm and died soon after rewarming. The four survivors (patients 2, 3, 4, and 5) maintained sinus rhythm during follow up of 3–13 months (mean 9 months).

No patient developed a complication that was thought to be a direct result of hypothermia. None developed additional ventricular arrhythmias. One patient (patient 3) was paced sequentially at 140 beats per minute because of a transient lowering of heart rate to 110 beats per minute. One other (patient 4) was sequentially paced at 150 beats per minute for four hours when her heart rate fell to 120 beats per minute. Pacing was stopped because neither blood pressure nor urine output improved. No other patient was electively paced during hypothermia. There was no change in the arterial blood pH during cooling in any patient (mean 7·38 (0·09) before cooling and 7·45 (0·05) during cooling, $p > 0·1$) and none developed metabolic acidosis owing to cooling. One patient (patient 2) had pulmonary hypertensive crises on rewarming. He did not have pulmonary hypertensive episodes before

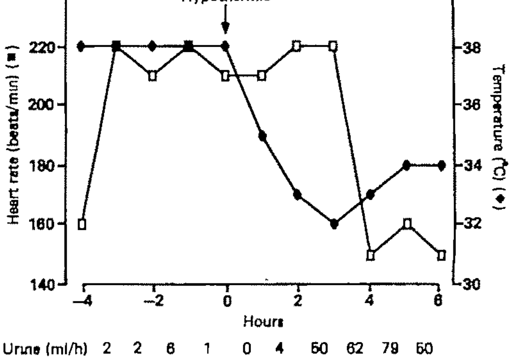


Figure 5 Effect of hypotherma on the heart rate and urine output in patient 3. Heart rate fell to 150 beats per minute when the core temperature reached 32°C. Urine output improved soon after hypothermia was started.

or during hypothermia. He also had a chest infection caused by *Staphylococcus aureus* at the time of rewarming. Rewarming was uneventful in patients 3, 4, and 5. Soon after rewarming patient 3 developed a chest infection caused by *Klebsiella* which led to ventilatory support being prolonged. Both patients 2 and 3, however, had been on assisted ventilation for eight and six days respectively at the time of diagnosis of the chest infection.

Discussion

Hypothermia reduces the automaticity of cardiac pacemaker cells and therefore may be valuable in the treatment of ectopic focus tachycardias. Persistent tachycardia may lead to haemodynamic deterioration, particularly in children with congenital heart defects. Though hypothermia in normal subjects is known to reduce cardiac output and increase systemic vascular resistance[8] it also reduces the oxygen demand so that the oxygen supply-demand balance is unaffected, provided the shivering response to hypothermia has been abolished by the use of paralysis and artificial ventilation.

His bundle tachycardia after heart surgery in children is often self-limiting.[3] Nevertheless, it is often difficult to control, causes acute haemodynamic instability, and can be fatal.[2,3] It is unresponsive to most conventional forms of treatment.[3,9] Digoxin,[2] propafenone,[10] and flecainide[9] have been reported to reduce the tachycardia rate to some extent. Both flecainide and propafenone, however, have a negative inotropic effect and there is no ideal drug or electrical treatment.

Bash *et al* reported the successful use of hypothermia in three infants[5] and Guccione *et al* reported it in two.[6] All had His bundle tachycardia after surgery for congenital heart disease, though none had undergone a Fontan procedure. Before they used a surface cooling blanket to produce systemic hypothermia Bash *et al* unsuccessfully used ice to the face alone in one case, ice to the face with digoxin and direct current cardioversion in one case, and digoxin and lignocaine in the other. Guccione *et al* reported that pharmacological treatment was unsuccessful but did not report the specific agents tried.

It has been suggested that His bundle tachycardia after cardiac surgery in children is unlikely to cause major haemodynamic deterioration at a rate below 200 beats per minute.[10] This has not been our experience. Loss of sinus rhythm and atrioventricular synchrony is poorly tolerated by patients after a Fontan operation.[11] His bundle tachycardia, even at rates of about 180 beats per minute, was poorly tolerated by our two patients who had modified Fontan operations. The period of hypothermia was relatively short (48 hours) in both. All three infants reported by Bash *et al* regained sinus rhythm after rewarming after periods of hypothermia ranging from four to 24 hours,[5] whereas both children reported by Guccione *et al* did so while still being cooled 12 and 42 hours after the start of hypothermia.[6] Two of our patients regained sinus rhythm during the cooling phase and the other two did so after rewarming. In retrospect, rewarming may have been attempted too early in the two patients who had modified Fontan procedures. A longer duration of cooling may have made the resumption of sinus rhythm more likely. R wave synchronised atrial pacing has been described as an adjunct to hypothermia in the management of postoperative His bundle tachycardia[12] and may be especially useful in the management of this condition after Fontan type operations.

In the neonate with ectopic atrial tachycardia, cooling was attempted only after other measures, both invasive and non-invasive, had failed. Hypothermia was successful in producing haemodynamic stability while he was waiting for operation. He never regained sinus rhythm.

Induction of hypothermia is simple and we did not recognise any unwanted side effects. The occurrence of pulmonary hypertensive crises during rewarming in one patient, a 7 month old infant who had undergone repair of a large ventricular septal defect, was thought to be related more to a chest infection than to the rewarming process. We were concerned that there may be a link with infection, which occurred in two of our patients. Both of them, however, had prolonged endotracheal intubation together with artificial ventilation and suboptimal cardiac output. In view of the complexity of their postoperative course we believe that a direct relation between hypothermia and infection cannot be established.

Moderate hypothermia can be used safely to manage children with His bundle tachycardia after cardiac surgery. It seems to slow the arrhythmia rate and so improve haemodynamic state. This may contribute to restoration of sinus rhythm or buy time before the arrhythmia resolves spontaneously. It may also produce similar benefit in other forms of automatic tachycardia and be useful as an adjunct to electrical or pharmacological treatment.

1 Gillette PC. Evolving concepts in the management of congenital junctional ectopic tachycardia. *Circulation* 1990,81.1713–4.
2 Grant JW, Serwer GA, Armstrong BE, Oldham HN, Anderson PAW. Junctional tachycardia in infants and children after open heart surgery for congenital heart disease *Am J Cardiol* 1987;59·1216–8
3 Gillette PC. Diagnosis and management of post-operative junctional ectopic tachycardia. *Am Heart J* 1989,118 192–4.
4 Hicks CE, McCord WC, Blount SG. Electrocardiographic changes during hypothermia and circulatory occlusion. *Circulation* 1956;13.21–8.
5 Bash SE, Shah JJ, Albers WH, Geiss DM. Hypothermia for the treatment of post surgical greatly accelerated junctional ectopic tachycardia. *J Am Coll Cardiol* 1987; 10.1095–9.
6 Guccione P, Papa M, Pasquini L, *et al* Junctional ectopic tachycardia after paediatric cardiac surgery; successful treatment with hypothermia [abstract]. *Eur Heart J* 1989;10:105.
7 Southall DP, Richards J, Mitchell P, Brown DJ, Johnston PGB, Shinebourne EA. Study of cardiac rhythm in healthy newborn infants. *Br Heart J* 1980;43:14–20.
8 Sealy WC Hypothermia. Its possible role in cardiac surgery. *Ann Thorac Surg* 1989;47:788–91.
9 Wren C, Campbell RWF. His bundle tachycardia—arrhythmogenic and antiarrhythmic effects of therapy *Eur Heart J* 1987,8:647–50.
10 Garson A, Moak JP, Smith RT, Norton JB. Usefulness of intravenous Propafenone for control of post-operative junctional ectopic tachycardia. *Am J Cardiol* 1987; 59:1422–4
11 Weber HS, Hellenbrand WE, Kleinman CS, *et al*. Predictors of rhythm disturbances and subsequent morbidity after the Fontan operation *Am J Cardiol* 1989;64:762–7.
12 Till JA, Rigby ML, Rowland E. R Wave synchronised atrial pacing as an adjunct to the management of His bundle tachycardia after surgery [abstract]. *Br Heart J* 1990;64:91.

Br Heart J 1991;66:225-9

Atrial pacing as an adjunct to the management of post-surgical His bundle tachycardia

Jan A Till, Edward Rowland

Abstract

***Objective*—To examine the benefits of restoring atrioventricular synchrony to children with His bundle tachycardia after operation for congenital heart disease.**

***Design*—Review of clinical outcome of adopting the technique of R wave synchronised atrial pacing as an adjunct to the management of His bundle tachycardia from September of 1987 till June of 1990.**

***Patients*—Eleven consecutive children (aged between 3 days and 13 years) with haemodynamically significant His bundle tachycardia after cardiopulmonary bypass surgery.**

***Interventions*—Atrial pacing synchronised either manually or automatically to the R wave of the His bundle tachycardia was implemented so that atrial depolarisation preceded the following R wave by an appropriate PR interval.**

***Results*—An immediate and sustained increase in mean systemic blood pressure (average 15 mm Hg, range 6-30 mm Hg) was seen with the onset of atrial pacing in 10 of the 11 children. One child, who had undergone a Fontan procedure, developed atrial flutter shortly after the onset of atrial pacing and required direct current cardioversion. Four children died. Of the seven survivors, six have sustained sinus rhythm which returned between two and 10 days after the onset of tachycardia. One of the survivors has severe neurological impairment attributed to a period of low cardiac output during tachycardia; the others are alive and well. In those children who did badly the mean time between arrhythmia occurrence and the start of atrial pacing or cooling or both was nine hours; in those who did well it was one hour.**

***Conclusions*—Atrial pacing synchronous with the His bundle is a useful adjunct in the management of children with His bundle tachycardia after surgery for congenital cardiac disease.**

Departments of Paediatrics and Cardiology, National Heart and Lung Institute, London
J A Till
E Rowland

Correspondence to
Dr Jan A Till,
Department of Paediatrics,
Royal Brompton National Heart and Lung Hospital,
Sydney Street,
London SW3 6NP.

Accepted for publication
29 April 1991

His bundle tachycardia occurring soon after operation for congenital heart disease is associated with a high mortality and significant morbidity.[1 2] Rapid tachycardia rates combine with loss of atrioventricular synchrony to limit severely cardiac output. Management is difficult because the arrhythmia is unresponsive to conventional methods of treatment. Should the child survive, the natural history is one of spontaneous termination between three to eight days after surgery. Though antiarrhythmic drugs may be helpful their use is limited by the severe haemodynamic impairment that frequently accompanies this arrhythmia. Bash *et al* successfully controlled the tachycardia rate in three children with corporal cooling and these and other workers have used atrial pacing at a rate greater than that of the tachycardia to further increase cardiac output after the rate has been reduced.[3] We used a new technique to restore atrioventricular synchrony. We synchronised the atrial pacing to the R wave of the tachycardia so that atrioventricular synchrony was restored without a further increase in heart rate and we evaluated the success of this approach as an adjunct to other methods of controlling post-surgical His bundle tachycardia.

Patients and methods

Between September 1987 and June 1990 we treated 11 consecutive children for haemodynamically significant post-surgical His bundle tachycardia. Their ages ranged between three days and 13 years. All developed His bundle tachycardia in the immediate postoperative period after operation for various congenital anomalies (table 1). Four children underwent complete correction of tetralogy of Fallot, two correction of double outlet right ventricle with subaortic ventricular septal defect, one patch closure of ventricular septal defect, one complete repair of atrioventricular septal defect, one complete repair of common arterial trunk with a homograft, one a mitral valvuloplasty for a dysplastic mitral valve, and one a Fontan procedure for tricuspid atresia. All operations were performed on cardiopulmonary bypass and were considered a "successful" repair by the surgeon at the time of operation. Two children (patients 1 and 5) developed complete atrioventricular block during surgery. Complete atrioventricular block was diagnosed by the presence of atrioventricular dissociation with a ventricular rate slower than and independent of that of the atria. His bundle tachycardia was diagnosed within six hours of surgery in seven of the children, within 12 hours in a further three, and in one child His bundle tachycardia developed 30 hours after operation. The two children who

Table 1 Patient details at onset of His bundle tachycardia

Case No	Age	Diagnosis	Surgery	HBT rate (beats/min)	Inotropic support	VA conduction
1	3 days	Dysplastic mitral valve	Repair	210	Dopamine, adrenaline	—
2	7 wk	VSD	Patch	205	Dopamine, isoprenaline	+
3	6 mnth	DORV	C	240	Dopamine, adrenaline, dobutamine	—
4	8 mnth	TOF	C	230	Dopamine, adrenaline	—
5	9 mnth	TOF	C	200	Dopamine, adrenaline	—
6	11 mnth	TOF/AVSD	C	210	Dopamine, adrenaline	+
7	1 yr	AVSD	C	250	Dopamine	—
8	11 yr	TOF/VPS	C	190	Dopamine	—
9	13 yr	TA	Fontan	170	Dopamine, isoprenaline	—
10	15 mnth	DORV	C	215	Dopamine, isoprenaline, dobutamine, adrenaline	—
11	10 mnth	Truncus	C	230	Dopamine, dobutamine, adrenaline	—

AVSD, atrioventricular septal defect; C, complete correction, DORV, double outlet right ventricle with subaortic ventricular septal defect, HBT, His bundle tachycardia, VSD, ventricular septal defect; TOF, tetralogy of Fallot, TA, tricuspid atresia, Truncus, common arterial trunk, VPS, valvar pulmonary stenosis

had previously had complete atrioventricular block developed His bundle tachycardia at 12 and 30 hours. Diagnosis of His bundle tachycardia was made from the surface electrocardiogram in most children and confirmed when necessary by recordings from atrial or ventricular electrodes (fig 1). The criteria for diagnosis were (*a*) heart rate greater than the 98th percentile for age, (*b*) a QRS configuration in tachycardia similar to that in sinus rhythm or to that with atrial pacing, and (*c*) the presence of atrioventricular dissociation with a ventricular rate greater than the atrial rate or retrograde ventriculo-atrial conduction. The maximum rate of tachycardia ranged from 170 beats/minute to 280 beats/minute (mean 216). All patients developed a severe low cardiac output with the onset of tachycardia and seven were oliguric with a urine output less than 1 ml/kg/hour. Initial management varied because it was undertaken by the doctor in charge of intensive care. All were treated with inotropic drugs to support a falling blood pressure. These included dopamine, dobutamine, adrenaline, and isoprenaline. A mean of 2·2 inotropic drugs were being given when His bundle tachycardia was recognised. All patients were receiving routine antibiotic treatment of flucloxacillin and gentamicin.

Eight children were initially treated with antiarrhythmic drugs. Amiodarone was used in six (5 mg/kg intravenously over 20 minutes) followed by a continuous infusion (15 mg/kg/day) and resulted in a reduction of tachycardia rate in five but failed to restore sinus rhythm in any child. One child who became hypotensive 10 minutes after the administration of amiodarone was given an intravenous bolus of calcium which precipitated ventricular fibrillation. One child was given flecainide (2 mg/kg intravenously over 10 minutes) and again this reduced the tachycardia rate but without return to sinus rhythm. An intravenous infusion of flecainide was therefore continued for a further 36 hours. Digoxin (standard intravenous loading dose for age followed by a maintenance regimen) was given to three without an immediately recognisable beneficial effect. One child was cardioverted with direct current without effect and in three further children atrial overdrive pacing, used in an attempt to terminate the arrhythmia and regain sinus rhythm, was unsuccessful. Ten children were surface cooled to a core temperature of 32°C with cooling blankets and ice packs. In all patients we used vecuronium to achieve paralysis and chloral hydrate or midazolam for sedation.

Atrial pacing was used to restore atrioventricular synchrony in all 11 children. The atrial pacing stimulus was synchronised with the R wave of the tachycardia either manually or automatically so that atrial depolarisation preceded ventricular depolarisation by a physiological atrioventricular interval. Initially we manually adjusted the relation of the atrial pacing stimulus to the R wave of the successive QRS complex by means of a simple standard temporary pacing box and two atrial wires. Having recognised the success of the technique we produced the same effect automatically by using two stimulators in concert—one to receive the input from the ventricle and the other to pace the atrium after a preset delay. We achieved a similar result with a dual chamber analyser (Medtronic) when the ventricular temporary pacing wires were connected to the atrial input and the atrial wires were attached to the ventricular output in the VDD pacing mode with an atrioventricular delay set so that the atrial pacing stimulus preceded the subsequent QRS complex by an appropriate interval. In six children we used temporary epicardial pacing wires placed at operation. However, five children did not have epicardial atrial pacing wires on their return from the operating theatre. In three of these five we used an oesophageal electrode until pacing was shown to be effective, then the chest was reopened in two to place temporary epicardial wires and a temporary transvenous electrode

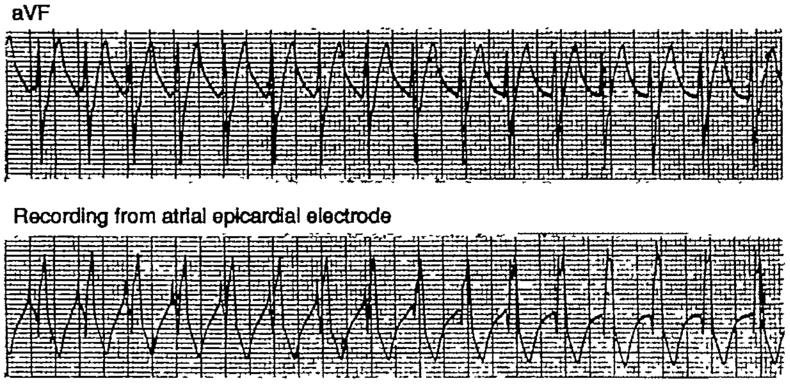


Figure 1 Surface electrocardiogram (lead aVF) and simultaneous recording from a temporary atrial electrode showing atrioventricular dissociation (after cooling).

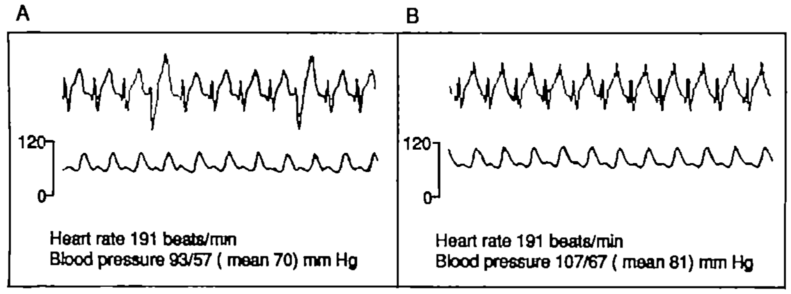

A
B
120
0
Heart rate 191 beats/min
Blood pressure 93/57 (mean 70) mm Hg
120
0
Heart rate 191 beats/min
Blood pressure 107/67 (mean 81) mm Hg

Figure 2 (A) Electrocardiogram and systemic blood pressure trace in patient 8 before onset of R wave synchronised atrial pacing. (B) Electrocardiogram and systemic blood pressure trace in the same patient after onset of R wave synchronised atrial pacing.

was positioned in the third. A further two children had their chest opened as an emergency procedure to relieve "atypical tamponade" and at that stage temporary epicardial atrial wires were placed.[4]

Results

Cooling was attempted in 10 children and was successful in eight. In one obese child (patient 9, 68 kg) attempts at cooling were abandoned after 10 hours when a core temperature of less than 35°C had still not been reached. An infant died before cooling was achieved. In the eight patients in whom cooling was successful a core temperature of 33°C or less was achieved between 30 minutes and four hours from onset. A reduction in tachycardia rate was achieved in all eight children. During this time three children became persistently mildly acidotic and two became hypoglycaemic but no other side effects were seen. It was not clear whether the metabolic disturbance resulted directly from a low cardiac output state or arose as a consequence of cooling. Cooling was maintained for up to seven days (mean 3·8 days). Coincident with cooling atrial pacing was used to restore atrioventricular synchrony. Cardiac output was not measured directly but mean blood pressure increased immediately with onset of atrial pacing (average increase in mean blood pressure 15 mm Hg, range 6–30 mm Hg) in 10 of the 11 children and was sustained (fig 2). Urine output, assessed over the three hour period before pacing and the three hour period after the onset of pacing, increased in six. In two children the urine output had already fallen to zero and there was no increase in urine output despite an apparent improvement in haemodynamic state; in three others the urine output remained low (table 2). The haemodynamic improvement allowed a slow withdrawal of inotropic drugs in nine children over the ensuing 24 hours. In one child atrial flutter developed within the first hour of starting atrial pacing (fig 3). This was the child who had undergone a Fontan procedure for tricuspid atresia (patient 9). At the time of pacing this child had a central venous pressure of 18 mm Hg. The atrial flutter rate was 300 beats/minute, a rate greater than that of the His bundle tachycardia, and it was conducted to the ventricle at a rate of 300 beats/minute. This new arrhythmia resulted in further haemodynamic compromise and it was treated immediately with direct current cardioversion. Atrial flutter was terminated; His bundle tachycardia resumed and despite the resumption of atrial pacing atrial flutter was not seen again.

The underlying rate and rhythm were assessed regularly. Atrial pacing was stopped at least daily to establish whether the child could manage without pacing. Similarly, after haemodynamic stability had been achieved the child was rewarmed at intervals to see whether he would tolerate a higher temperature. Seven children survived. Of these, six returned to sinus rhythm after 2–10 days (mean 6 days) and one returned to a slow junctional rhythm. One survivor suffered extensive neurological damage attributed to low cardiac output. Four of the 11 children died. One died shortly after the tachycardia was recognised and neither cooling nor atrial pacing had been well established. We think that this child had had unrecognised episodes of His bundle tachycardia four hours after the operation. Atrial pacing and cooling were delayed until 20 hours. Three further children died despite effective atrial pacing and cooling. Though the small numbers do not allow proper statistical analysis an important factor contributing to outcome in some children seemed to be the length of time the child was in His bundle tachycardia before atrial pacing or cooling or both were started. In children who are alive and well (patients 2, 3, 5, 7, 10, and 11) the mean time between the occurrence of arrhythmia and the start of pacing and cooling was approximately one hour. In contrast, in the group who did badly (patients 1, 4, 6, 8, and 9) the mean time between arrhythmia occurrence and the start of pacing and cooling was nearly nine hours.

Table 2 Treatment details

Case No	*Time of occurrence after surgery (h)*	*Time of recognition after surgery (h)*	*Time of pacing (h)*	**Urine output before pacing (ml/kg/h)*	**Urine output after pacing (ml/kg/h)*	*Antiarrhythmic drugs*
1	12	18	18	0·5	2	—
2	3	3	3	1	1·8	—
3	0	0	2·5	1·4	4	Amiodarone
4	4	20	20	<1	0	Amiodarone
5	30	30	30	0·4	2·4	Digoxin, amiodarone
6	2	4	2	0	0	—
7	10	12	14	<1	<1	Flecainide
8	0	22	22	1	<1	Digoxin, amiodarone
9	4	4	4	>1	<1	Amiodarone
10	3	3	5	<1	>1	Digoxin, adenosine
11	4·5	4·8	5·5	0·6	1·3	Amiodarone, adenosine

*Urine output was assessed over a three hour period before and after the start of atrial pacing.

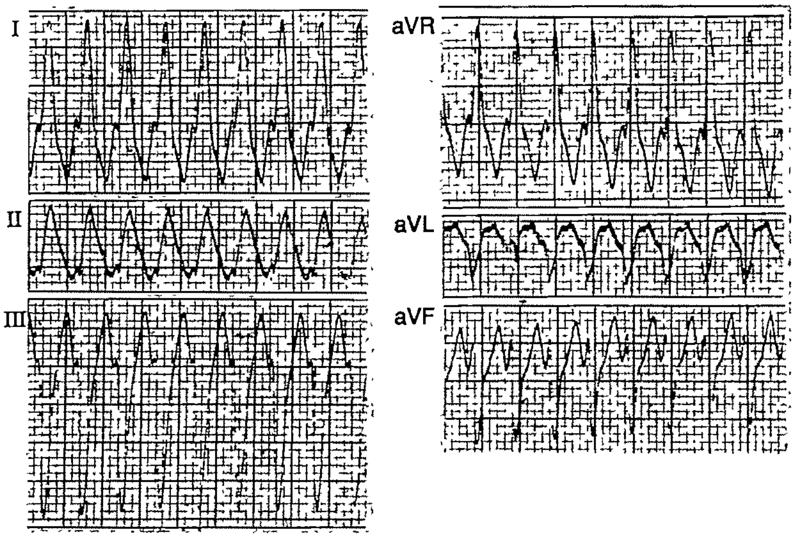


Figure 3 Electrocardiogram (limb leads) in patient 9 showing atrial flutter. (300 beats/min).

Discussion

His bundle tachycardia occurring in the immediate postoperative period after repair of congenital heart disease is a life-threatening complication of surgery. The poor outcome results from the loss of atrioventricular synchrony and a high tachycardia rate. The incidence of His bundle tachycardia after cardiac surgery in children is unknown but in a retrospective review of 154 children undergoing open heart surgery from 1983 to 1984 Grant *et al* identified 12 cases with haemodynamically significant His bundle tachycardia.[5] The arrhythmia is thought to result from an ectopic "automatic" focus within the His bundle. Evidence to support the automatic nature of the arrhythmia includes its tendency to "warm up" and its resistance to both overdrive pacing and direct current cardioversion.

At a cellular level the tachycardia may result from delayed afterdepolarisations.[6] It has been suggested that cellular damage may occur at surgery because many patients have had surgery to the upper ventricular septum though occasionally His bundle tachycardia can also occur in patients undergoing cardiac operations involving surgery remote from the bundle of His.[7 8] It is of interest that two patients developed His bundle tachycardia after earlier transient complete atrioventricular block. This supports the idea that His bundle tachycardia arises as a result of traumatic damage to the His bundle during surgery. In both patients His bundle tachycardia seemed to develop during recovery of complete atrioventricular block; intact atrioventricular conduction during His bundle tachycardia was demonstrable with atrial pacing in both children. One child later died but the other recovered sinus rhythm without further evidence of complete atrioventricular block.

His bundle tachycardia, whether occurring in the immediate postoperative period or as a congenital arrhythmia in an otherwise structurally "normal" heart, is largely refractory to conventional antiarrhythmic drugs. Grant *et al* described a beneficial response (a small decrease in rate) to digoxin in six of a group of eight patients after operation. However, this favourable response was not seen by others. Garson *et al* did not see any beneficial response in seven similar children 90 minutes after loading with digoxin; and Sholler *et al* noted little response in nine of 18 children, a small decrease in rate in six, and an increase in tachycardia rate in three patients treated with digoxin alone.[9 10] In both types of His bundle tachycardia the success of propranolol and verapamil has been limited; indeed an increase in tachycardia rate with consequent haemodynamic collapse has been described after administation of verapamil in the congenital form of the arrhythmia.[9 11 12] These workers suggested that the increase in arrhythmia rate seen after intravenous verapamil may represent a reflex response to vasodilatation.

More recently some success has been claimed with the newer class 1c drugs, propafenone and flecainide. There are good theoretical reasons why these agents should suppress this tachycardia because they are potent depressants of automaticity in vitro. Administration of these drugs to critically ill children may be difficult, however, because of their known negative inotropic properties. Garson *et al* used propafenone to treat seven children with postoperative His bundle tachycardia. The His bundle tachycardia rate was significantly reduced but Garson *et al* recommended slow administration because they saw a significant fall in blood pressure that required a plasma infusion to restore blood pressure to an acceptable level.[9] Wren and Campbell reported a patient in whom congenital His bundle tachycardia responded to flecainide.[13] Amiodarone has also been used in the management of both congenital and postoperative His bundle tachycardia. Villain *et al* report the successful reduction of rate to below 150 beats/minute in eight of 14 children with

Table 3 Outcome

Case No	Cooling time (days)		Pacing time (days)		Outcome	Resolution of HBT (days)	Rhythm
1	Yes	3	Yes	3	Died	—	—
2	Yes	5	Yes	6	Alive/well	5	SR
3	Yes	5	Yes	5	Alive/well	6	SR
4	NA	—	NA	—	Died	—	—
5	Yes	7	Yes	7	Alive/well	6	SR
6	Yes	1	Yes	1 5	Died	—	—
7	No	—	Yes	1 5	Alive/well	10	SR
8	Yes	1	Yes	1	Died	—	—
9	NA	—	Yes	2	Alive/NI	2	JR
10	Yes	5	Yes	5	Alive/well	7	SR
11	Yes	4	Yes	4	Alive	4	SR

JR, junctional escape rhythm, NA, not achieved; NI, neurological impairment; SR, sinus rhythm.

congenital arrhythmia.[14] When we used amiodarone in post-surgical patients we reported a reduction in tachycardia rate in four of seven patients though in no case did amiodarone terminate tachycardia and restore sinus rhythm.[2]

Bash *et al* recently reported a novel approach to management—the use of corporal cooling in three young children who developed His bundle tachycardia postoperatively.[3] Hypothermia has long been recognised as a means of suppressing the automaticity of cells but has only recently been applied clinically. In our small series cooling seemed to be successful in bringing about a controlled decrease in tachycardia rate and was accompanied by few side effects. A criticism of our study is that we used several treatments at the same time. We believed that it was unethical to stop a treatment that might prove beneficial in such a life-threatening condition in order to evaluate properly another new treatment. Therefore the three children in whom digoxin had been started continued to receive digoxin throughout the evaluation period. Similarly, amiodarone was continued in four children and flecainide in one. The decisions to cool and pace the child were often made at the same time but cooling took longer to achieve. The effects of atrial pacing were therefore assessed at normothermia in some children. Even without cooling there was an increase in mean blood pressure with a steady decline in heart rate which we attributed to an improvement in haemodynamic state caused by pacing. Also in some cases cooling was achieved first because R wave synchronised atrial pacing required a physician familiar with pacing to be on site. In these patients cooling was associated with a stabilisation in haemodynamic state and a steady decline in heart rate in most patients. An additional beneficial effect was seen when pacing started.

Waldo and colleagues described a different approach to the problem of His bundle tachycardia.[8] They reported a case of post-surgical His bundle tachycardia in which the mechanical ventricular rate was halved by paired ventricular pacing. The highly refractory nature of His bundle tachycardia has led some clinicians to ablate permanently the His bundle in children with the congenital form.[15 16] This more radical and permanent approach results in complete atrioventricular block and necessitates implantation of a permanent pacemaker. None of the treatments previously described, however, has returned the child to sinus rhythm and therefore even if the rate is reduced there remains atrioventricular dissociation or, at worst, ventriculoatrial conduction resulting in atrial contraction almost coincident with ventricular contraction. Though cardiac output in small children is predominantly rate dependent, cardiac output can be significantly increased in the sick heart by the addition of atrial contraction at the correct time in the cardiac cycle. We restored atrioventricular synchrony to these patients without a further increase in heart rate, and in our group the restoration of atrioventricular synchrony was associated with an immediate and beneficial response in 10 of the 11 children. His bundle tachycardia is unlike the more common arrhythmias seen in childhood in that the rate is variable because it is highly dependent upon autonomic tone. In these children it is important to minimise any further reflex increase in tachycardia rate by preventing falls in blood pressure and by limiting the use of sympathomimetic drugs. Our results confirm that early recognition followed by vigorous appropriate management are key features in avoiding this vicious cycle of deterioration in these patients. They also emphasise the need for the routine placement of temporary pacing wires after surgery for congenital heart disease even if complete atrioventricular block is not present. A treatment that can take effect immediately, is without adverse actions, and can produce a beneficial response in cardiac output has considerable advantages.

1 Krongrad E Postoperative arrhythmias in patients with congenital heart disease. *Chest* 1984;85:107–13.

2 Till JA, Rowland E, Rigby M. His bundle tachycardia. an important cause of postoperative mortality and morbidity In Crupi G, Parenzan L, Anderson RH, eds. *Perspectives in paediatric cardiology* New York: Futura Publishing Company, 1990,2(3).269–72.

3 Bash S, Shah JJ, Albers WH, Geiss DM. Hypothermia for the treatment of postsurgical greatly accelerated junctional ectopic tachycardia. *J Am Coll Cardiol* 1987,10 1095–9

4 Shore DF, Capuani A, Lincoln C Atypical tamponade after cardiac operation in infants and children *J Thorac Cardiovasc Surg* 1982,83·449–52.

5 Grant JW, Serwer GA, Armstrong BE, Oldham HN, Anderson PAW Junctional tachycardia in infants and children after open heart surgery for congenital heart disease. *Am J Cardiol* 1987;59.1216–8

6 Rosen MR, Fisch C, Hoffman BF, Danilo P, Lovelace DE, Knoebel SB Can accelerated atrioventricular junctional escape rhythms be explained by delayed afterdepolarizations? *Am J Cardiol* 1980;45·1272–84

7 Garson A, Gillette PC. Junctional ectopic tachycardia in children· electrocardiology, electrophysiology and pharmacological response *Am J Cardiol* 1979;44·298–302

8 Waldo AL, Krongrad E, Kupersmith J, Levine R, Bowman FO, Hoffman BF Ventricular paired pacing to control rapid ventricular heart rate following open heart surgery. *Circulation* 1976,53:176–81.

9 Garson A, Moak JP, Smith RT, Norton JB Usefulness of intravenous propafenone for control of postoperative junctional ectopic tachycardia *Am J Cardiol* 1987, 59 1422–4

10 Sholler GF, Walsh EP, Mayer JE, Saul JP, Gamble WJ, Lang P. Evaluation of staged treatment protocol for postoperative rapid junctional tachycardia [abstract] *Circulation* 1988;78(suppl 11).597.

11 Bucknall C, Ladusans E, Tynan MJ, Curry PVL Ventricular tachycardia masquerading as supraventricular tachycardia. management of His bundle tachycardia [abstract] *Am Heart J* 1967;73 814

12 Karpawich PP. Junctional ectopic tachycardia in an infant electrophysiologic evaluation. *Am Heart J* 1985;109. 159–60.

13 Wren C, Campbell RWF. His bundle tachycardia-arrhythmogenic and antiarrhythmic effects of therapy *Eur Heart J* 1987,8:647–50.

14 Villain E, Vetter VL, Garcia JM, Herre J, Cifarelli A, Garson A Evolving concepts in the management of congenital junctional ectopic tachycardia. *Circulation* 1990;81·1544–9.

15 Gillette PC, Garson A, Coburn JP, *et al* Junctional automatic ectopic tachycardia new proposed treatment by transcatheter His bundle ablation *Am Heart J* 1983; 106 619–23

16 Gillette PC. Diagnosis and management of postoperative junctional ectopic tachycardia. *Am Heart J* 1989,118 192–4.

Br Heart J 1991;66:230–7

Dynamics of ventricular repolarisation in the congenital long QT syndromes

Nicholas J Linker, A John Camm, David E Ward

Department of Cardiological Sciences, St George's Hospital Medical School, London
N J Linker
A J Camm
D E Ward

Correspondence to
Dr Nicholas J Linker,
Department of Cardiological Sciences, St George's Hospital Medical School,
Cranmer Terrace, London
SW17 0RE.

Accepted for publication
26 March 1991

Abstract

Patients with congenital QT interval prolongation are at risk of ventricular arrhythmias and sudden death. It has been suggested that the susceptibility to arrhythmias in these syndromes may be related to the abnormal dynamics of ventricular repolarisation. The dynamics of ventricular repolarisation, including assessment of the effect of changing heart rate on the QT interval and the duration of the right ventricular monophasic action potential, were studied in eight patients with congenital long QT syndromes. The effects of altered sympathetic tone on these dynamics were investigated with isoprenaline, propranolol, and left stellate ganglion block. The rate adaptation of the QT interval was abnormal in only a few patients and in some patients this feature may be related to the severity of the condition. These abnormalities may be exaggerated by isoprenaline and lessened by propranolol and left stellate ganglion block. Monophasic action potential dynamics were normal in all patients.

The hypothesis that impaired QT rate adaptation may play a role in the genesis of ventricular arrhythmias in these syndromes is not, in general, supported by the present data. However, in patients with impaired adaptation the normalisation of QT dynamics after β blockade and left stellate ganglion block was consistent with the efficacy of these forms of treatment.

The QT interval of the electrocardiogram reflects the total duration of electrical activity in the ventricles. Two syndromes are associated with a primary hereditary prolongation of the QT interval. In both the Jervell and Lange-Nielsen and the Romano Ward syndromes there is usually a family history of syncopal episodes caused by ventricular tachycardia, the most common of which is torsade de pointes, and a family history of sudden cardiac death.[1–3] It has been suggested that the susceptibility to arrhythmias in these syndromes may be related to an absence or alteration of the normal QT shortening in response to an increase in heart rate.[4] We studied the dynamics of ventricular repolarisation, as measured by the QT interval and ventricular monophasic action potential duration, in patients with congenital QT interval prolongation and assessed the effects on these dynamics of alterations in sympathetic tone.

Table 1 Patient characteristics

Patient	*Sex*	*Age*	*Diagnosis*	*Symptoms*	*Documented torsade de pointes*
1	F	17 yr	RW	Syncope × 3	+
2	M	15 mnth	JLN	Syncope > 300	+
3	M	3 yr	JLN	Syncope × 15	+
4	F	7 yr	JLN	Syncope × 4	+
5	M	18 mnth	JLN	None	−
6	F	19 yr	RW	Syncope × 1	+
7	F	20 yr	RW	Syncope × 3	+
8	F	43 yr	RW	Syncope > 20	+

RW, Romano Ward syndrome; JLN, Jervell Lange-Nielsen syndrome.

Patients and methods

We studied eight patients (three male, five female), mean age 14 years (range 15 months to 43 years) (table 1). Four patients (numbers 2 to 5) had sensorineural deafness consistent with the Jervell and Lange-Nielsen syndrome; patients 2 and 3 came from the same family as did patients 4 and 5. Patient 1 had two sisters who died suddenly aged 16 and 20 years, both with a history of syncope. Patients 6, 7, and 8 had no family history of syncope or sudden death. Patient 5 (brother of patient 4) was found to have a long QT interval on routine electrocardiographic screening. Two patients (6 and 8) had previously been diagnosed as having either hysterical or epileptiform collapses on several occasions. Seven patients had documented torsade de pointes at the time of syncope.

No patient was taking any antiarrhythmic medication (including β blocking agents) at the time of the study. Table 2 gives QRS durations, QT intervals, QTc values, and cycle lengths in sinus rhythm. Four electrocardiographic leads (I, aVF, V1, and V6) were recorded at paper speeds of 50 or 100 mm/s. This configuration was preset by the recorder and remained constant throughout the study. The QT interval was measured from lead V1, because this provides a close approximation to the maximum QT interval in any lead.[5] During sinus rhythm and atrial pacing the QT interval was measured from the start of the QRS complex to the end of the T wave. During ventricular pacing the QT interval was measured from the ventricular pacing artefact or the beginning of the paced QRS complex (if there was stimulus latency) to the end of the T wave. The end of the T wave was defined as the point of return of the T wave to baseline.[6] There is no accepted definition of U waves in the long QT syndromes. In the presence of bizarre and often

Table 2 QRS duration, QT interval, and QTc values in all patients before and after propranolol

		Baseline (sinus rhythm)			*Propranolol (sinus rhythm)*		
Patient	*QRS duration (sinus rhythm) (ms)*	*QT (ms)*	*Cycle length (ms)*	*QTc* (s$^{1/2}$)	*QT (ms)*	*Cycle length (ms)*	*QTc* (s$^{1/2}$)
1	90	500	930	0·520	480	980	0·485
2	80	645	600	0·835	380	600	0·490
3	90	440	680	0·535	435	680	0·530
4	80	580	680	0·705	520	810	0·580
5	85	360	560	0·480	360	560	0·480
6	90	500	950	0·515	520	950	0·535
7	90	360	480	0·520	390	650	0·485
8	110	470	720	0·555	505	810	0·560

changing T wave configuration it is not possible clearly to distinguish between the T and U waves. Thus all our measurements were made to the end of total repolarisation as defined above. During ventricular pacing the T wave was always inscribed as a simple curve with no U waves or multiphasic components.

The QTc values were calculated from the formula adapted by Taran and Szilagyi[7] from a formula devised by Bazett.[8] Dimensional analysis of the Taran and Szilagyi formula shows the units of QTc to be s$^{1/2}$.[9]

The procedure was performed after the patient or a parent had given informed consent to an electrophysiology study. In all patients a 6 French gauge bipolar pacing electrode was inserted via the right femoral vein and positioned at the right ventricular apex to permit ventricular pacing. In five patients (1 and 4 to 7), a 7 French gauge silver/silver chloride monophasic action potential contact electrode was introduced via the right femoral vein and positioned at the right ventricular apex. In one patient (case 1) a monophasic action potential electrode was also positioned at the left ventricular apex via the right femoral artery. In one patient (case 6) a monophasic action potential electrode and a pacing electrode were positioned in the right atrium to allow atrial measurements to be made. The signals from the monophasic action potential electrodes were processed by a custom built AC amplifier with a band width of 0·025 to 500 Hz (−3 dB) and recorded on a Siemens-Elema Mingograf 82 chart recorder at a speed of 50 or 100 mm/s together with four surface leads (leads I, aVF, V1, and V6). Pacing was performed with a Digitimer 4279 programmable stimulator. All measurements were made by two observers. The duration of the monophasic action potential was measured at 90% repolarisation (MAP$_{90}$) because it is difficult to determine the exact point of full repolarisation.

The QT interval and MAP$_{90}$ duration were determined during sinus rhythm in all patients. In all patients ventricular pacing was performed for 10 seconds from the right ventricular apex at a cycle length that was 50 ms shorter than the intrinsic cycle length of the patient. The QT interval and MAP$_{90}$ duration of the last paced beat were measured (fig 1). After a 30 second pause, the pacing train was repeated with the cycle length 20 ms shorter; the pacing trains were repeated at shorter cycle lengths until ventricular exit block occurred. All cycles with extrasystoles were discarded and repeated. Three patients (4, 6, and 8) received an infusion of isoprenaline at 4 μg/kg/min and in two of these (6 and 8) the protocol was repeated. The protocol was repeated 10 minutes after the injection of 0·2 mg/kg of propranolol in six patients and in one patient (case 8 who had asthma), after 5 mg of intravenous atenolol. In two patients (3 and 4) the protocol was repeated after left stellate ganglionectomy (including intravenous propranolol in patient 3) and in one patient (case 2) the protocol was repeated after a marcaine induced left stellate ganglion block.

In patient 1 the recordings were made from both right and left ventricles. In patient 6 the baseline protocol was performed with atrial pacing and recording atrial monophasic action potentials in addition to ventricular studies. In patients 6 and 8 the dispersion of right ventricular MAP$_{90}$ durations was determined by recording monophasic action potentials from four and six right ventricular sites respectively.

It was not possible to perform every protocol in all patients because this would have needed prolonged studies in very young children. In one patient who received isoprenaline (case 4) spontaneous torsade de pointes occurred repeatedly and the protocol was not completed. Only two patients underwent left stellate ganglionectomy and one left stellate ganglion block. The dispersion of monophasic action potentials was not routinely measured because this has been published previously.[10] The measurement of atrial monophasic action potentials was introduced late in the study as part of another continuing protocol.

Where appropriate all results were compared by a Student's paired *t* test.

Results

QT INTERVAL IN SINUS RHYTHM

All patients had a normal baseline QRS duration (mean (SD) 89 (9) ms) with a mean QT interval of 482 (99) ms at a mean cycle length of 700 (166) ms (90 (20) beats/minute) and an increased QTc (0·583 (0·012) s$^{1/2}$) (table 2). After β blockade with propranolol or atenolol there was no significant change in the mean QT interval (449 (66) ms), QTc value (0·518 (0·038) s$^{1/2}$), or cycle length (755 (157) ms, 90 (20) beats/minute). Three patients were given isoprenaline (cases 4, 6, and 8), after which there was a significant shortening of the QT

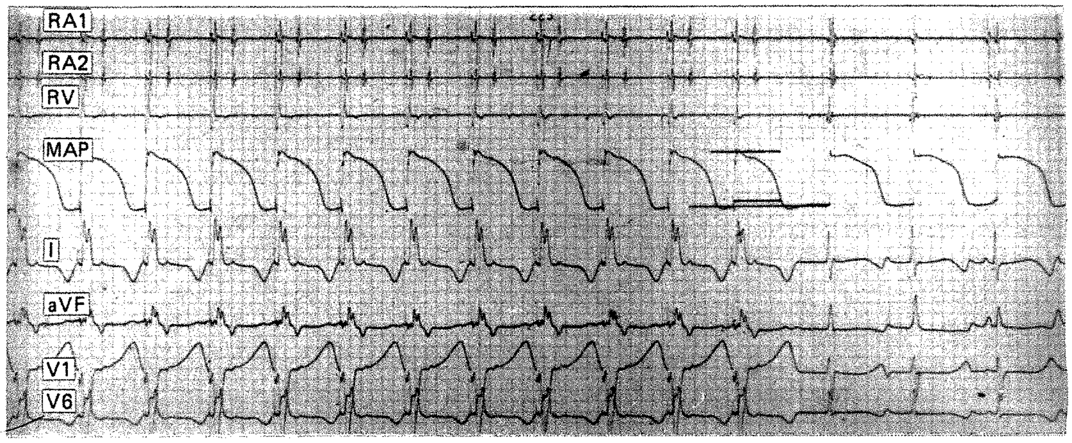


Figure 1 Recording of monophasic action potentials and QT interval during ventricular pacing in patient 4. For explanation of measurement see text. RA1, RA2, right atrial electrograms; RV, right ventricular electrogram; MAP, right ventricular monophasic action potential recording. Paper speed 100 mm/s.

interval (330 (56) ms $p < 0·05$), though this was in the presence of a shorter cycle length (438 (91) ms, p = NS) and there was no significant change in the QTc value (0·498 (0·032) $s^{½}$). In the two patients (cases 3 and 4) in whom left stellate ganglionectomy was performed there was no difference between values before and after ganglionectomy in the QT interval (440 and 580 ms *v* 460 and 580 ms), cycle length (680 and 560 ms *v* 560 and 780 ms), or QTc value (0·535 and 0·705 $s^{½}$ *v* 0·615 and 0·665 $s^{½}$).

MONOPHASIC ACTION POTENTIALS IN SINUS RHYTHM

In the patients in whom monophasic action potentials were recorded (cases 1 and 4 to 8) the baseline MAP_{90} duration was 363 (79) ms. Abnormalities in the configuration of monophasic action potentials, in particular "humps" on phase 3 of the monophasic action potential, were seen in three patients (cases 4, 7, and 8). In one patient (case 4) a spontaneous episode of torsades de pointe was recorded during the isoprenaline infusion, which showed that the first beat of the arrhythmia was not related to the "hump" (fig 2). After propranolol there was no significant change in MAP_{90} duration (353 (52) ms). In the three patients who received isoprenaline (cases 4, 6, and 8), there was a significant shortening in MAP_{90} duration (252 (51) ms, $p < 0·05$), though this was accompanied by a decrease in the sinus cycle length.

QT RATE ADAPTATION

The response of the patients' QT intervals to the ventricular pacing protocol was as follows. As the pacing rate was increased, there was a tendency for the QT interval to shorten (fig 3), though there was considerable variation between patients. In particular, patients 1 and 2 showed no adaptation of the QT interval to the faster pacing rates. In patient 1 (fig 3) the QT interval at a cycle length of 680 ms (540 ms) was shorter than at a pacing rate of 400 ms (580 ms). In patient 2 there appeared to be no rate adaptation, with the QT interval behaving in a haphazard fashion. Although the other patients tended to shorten their QT interval with decreasing pacing rate, the amount of decrease in QT interval was variable. For example, patient 8 showed very little change (100 ms decrease in QT interval over a pacing range of 600 to 260 ms) whereas patient 4 showed a 190 ms decrease in QT interval over the same pacing range.

In the two patients who received isoprenaline and had the protocol repeated, one (patient 8) showed no change in QT interval duration or dynamics. The other (patient 6) had normal baseline QT dynamics and a total loss of QT adaptation during the isoprenaline infusion

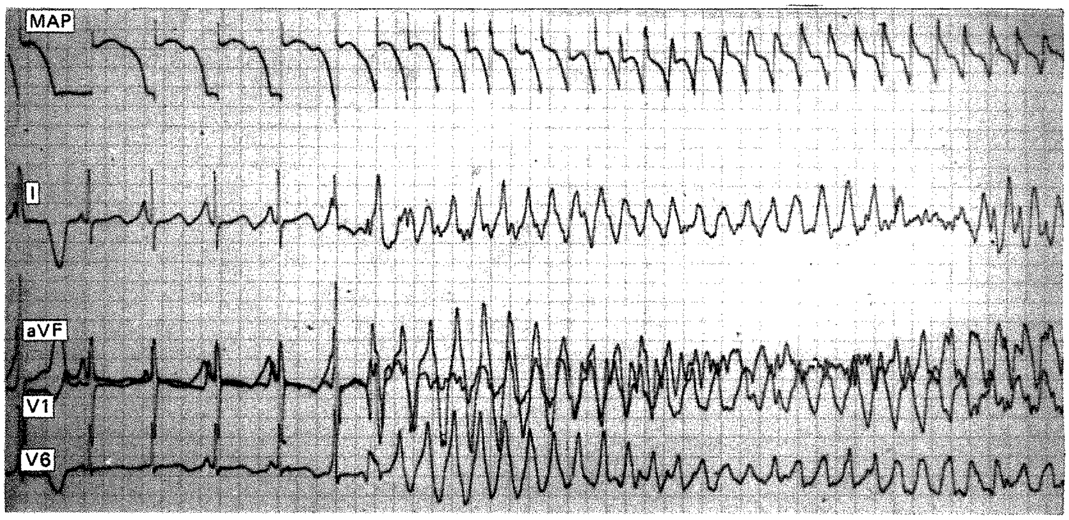


Figure 2 Spontaneous torsade de pointes in patient 4 during an isoprenaline infusion. The initiating beat of the arrhythmia occurs before the right ventricular monophasic action potential, suggesting that the abnormalities in the configuration of the monophasic action potential are not relevant to the initiation of the tachycardia. For further discussion see text. MAP, right ventricular monophasic action potential recording. Paper speed 50 mm/s.

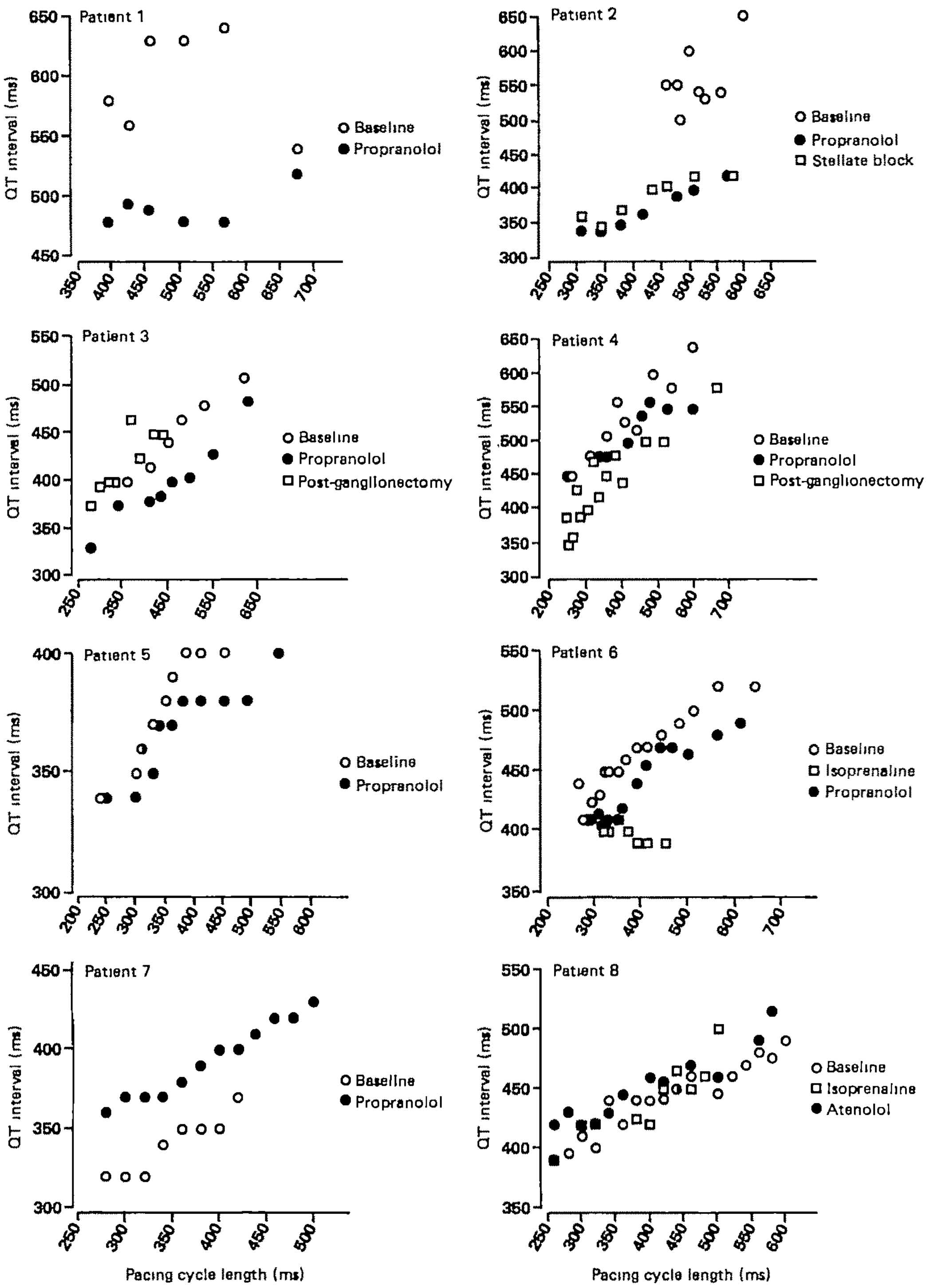


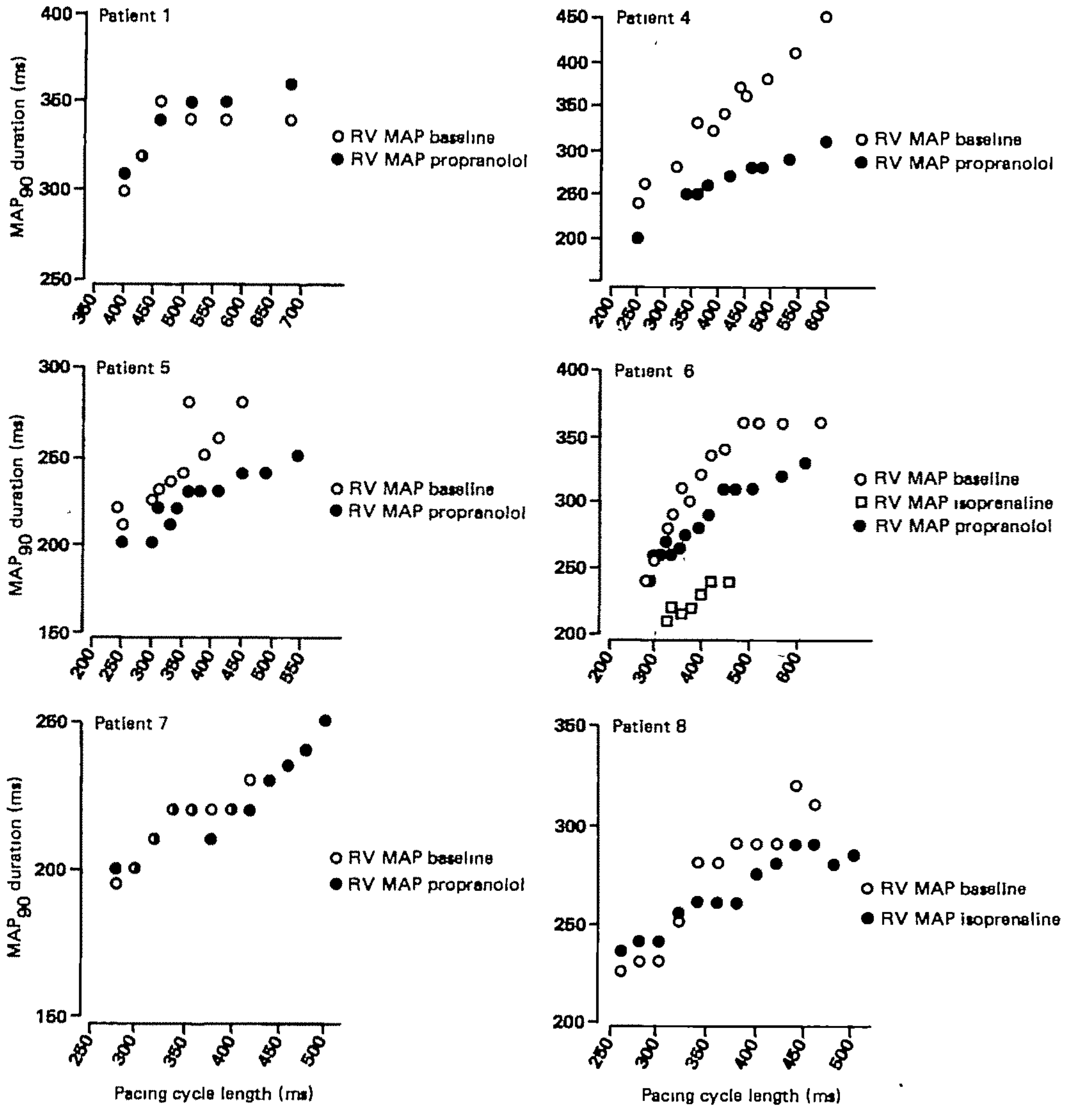
Figure 3 Rate adaptation of the QT interval in all eight patients with congenital long QT syndrome. For explanation see text.

with no change in QT interval over the 130 ms (55 beats/minute) change in pacing cycle length. After the isoprenaline infusion this patient was given an injection of propranolol and her QT dynamics reverted to their normal baseline state.

After β blockade there was no significant change in the paced QT intervals overall, although five patients (cases 1 to 3 and 5 and 6) showed a general shortening of their QT intervals, while patient 7 showed a lengthening of QT interval and patients 4 and 8 showed no change (fig 3). There was the same trend for the QT interval to shorten with increasing pacing rate and in particular patients 1 and 2, who showed no rate adaptation in the baseline study, displayed appropriate QT interval shortening.

The two patients who underwent left stellate ganglionectomy (cases 3 and 4) had normal QT dynamics during their baseline studies and there was no change in either QT interval or QT dynamics after the operation. The one patient (case 2) who underwent left stellate block after the propranolol injection showed no additional change in QT dynamics or QT interval. In all three patients torsade de pointes degenerating to ventricular fibrillation was induced when the left stellate ganglion was manipulated surgically or with a needle.

Figure 4 MAP$_{90}$ rate adaptation in patients 1 and 4 to 8. For explanation see text.



MONOPHASIC ACTION POTENTIAL RATE ADAPTATION

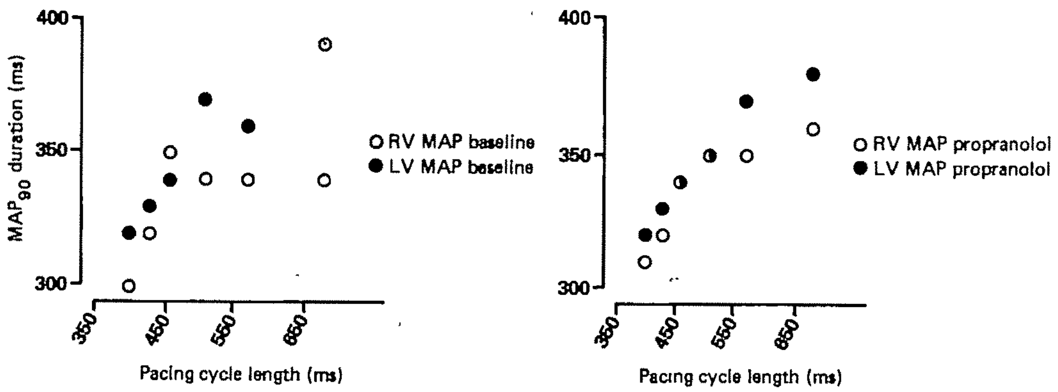
Ventricular monophasic action potentials were recorded during the ventricular pacing protocol in six patients (cases 1 and 4 to 8). In all patients, including those with altered QT dynamics, there was a decrease in MAP$_{90}$ duration as the pacing rate was increased (fig 4). The range of decrease in MAP$_{90}$ duration was variable—for example 50 ms in patient 1 (who had altered QT dynamics) and 210 ms in patient 4 (who showed normal QT dynamics). In the five patients in whom the study was repeated after propranolol (cases 1 and 4 to 7), there was no overall difference in MAP$_{90}$ duration: three patients (cases 4, 5, and 6) showed shortening of the MAP$_{90}$ duration, one patient (case 1) showed a slight increase in MAP$_{90}$ duration, and one patient (case 7) showed no change. After propranolol in all patients, the monophasic action potential dynamics remained similar to the baseline study.

Two patients had the protocol repeated during an isoprenaline infusion. One (patient 6) showed a shortening of the MAP$_{90}$ duration which was associated with 30 ms adaptation with increasing pacing rate (fig 4). This patient had no QT adaptation after isoprenaline. The other (patient 8) showed no change in MAP$_{90}$ duration or dynamics after isoprenaline (fig 4). One patient (case 1) had simultaneous right apical and left apical ventricular monophasic action potentials recorded (fig 5). Whereas the left ventricular MAP$_{90}$ duration was less than the right ventricular MAP$_{90}$ duration, both showed similar rate adaptation before and after propranolol. One patient (case 6) had right atrial monophasic action potentials recorded during atrial pacing (fig 6). Normal adaptation of the atrial MAP$_{90}$ duration to increasing atrial pacing rate[11] was seen in this patient.

DISPERSION OF MONOPHASIC ACTION POTENTIALS

Dispersion of MAP$_{90}$ duration was assessed in patients 6 and 8 by measurement of the right ventricular MAP$_{90}$ duration at four and six sites respectively during atrial pacing at a cycle length of 500 ms. In patient 6 the amount of dispersion was 50 ms (370 to 420 ms) and in patient 8 it was 65 ms (315 to 380 ms). In both patients the longest MAP$_{90}$ durations were recorded from the right ventricular mid septum; however, the shortest MAP$_{90}$ durations were recorded from the right ventricular inflow tract in patient 6 and from the free wall of the right ventricle in patient 8. These values for dispersion are excessive compared with normal values.[12 13]

Figure 5 Simultaneous right and left ventricular monophasic action potential recordings in patient 1 before and after propranolol.



Discussion

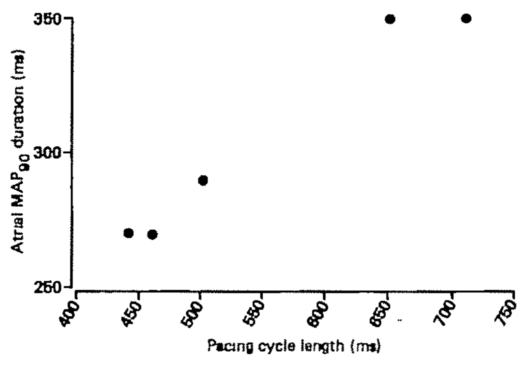
The dynamics of the QT interval have been evaluated in normal subjects, but not in patients with congenital long QT syndromes. Studies in patients or subjects unaffected by prolonged QT syndromes showed that the QT interval is dependent on heart rate and also on changes in the catecholamine sensitivity of the heart.[14,15] Other studies of changes in the QT interval with exercise showed an exponential relation between the QT interval and heart rate in normal subjects.[16,17] Studies to evaluate the dynamics of the paced QT interval with atrial[18] and ventricular pacing[18,19] showed that in normal subjects or in patients with complete heart block the QT interval shortened with increasing pacing rate. The relation between these two functions was curvilinear: with a linear relation between heart rates of approximately 70 and 120 beats/minute.[20,21]

Six of our eight patients with congenital QT prolongation showed an exponential or curvilinear pattern of QT rate adaptation. One (patient 2) of the two patients who showed no rate adaptation had a particularly severe manifestation of the syndrome with over 300 syncopal episodes. His resting QT interval was considerably prolonged (table 2) and he showed no rate adaptation (fig 3). It has been suggested that poor rate adaptation of the QT interval in patients with congenital long QT syndromes may increase the susceptibility to ventricular arrhythmias.[4] The failure of QT rate adaptation was considered to be due to a reduction or lack of rate-related shortening of the ventricular action potential. Thus there is an increased likelihood that a ventricular extrasystole will occur in this vulnerable period and produce a ventricular arrhythmia.[4] There is, however, no direct evidence for this hypothesis. Only two of the seven patients with documented torsade de pointes did not have evident rate adaptation. However, an increasing ventricular rate may be associated with an increase in U wave amplitude, a feature that often precedes the development of torsade de pointes.[22] Changes in the U wave amplitude, T wave alternans, and the occurrence of torsade de pointes often appear shortly after an abrupt increase in heart rate,[23] as in the present study, or can be elicited by other manoeuvres that increase sympathetic tone such as isoprenaline, as seen in patient 4 (fig 2), exercise,[24] or the Valsalva manoeuvre.[25]

The recording of monophasic action potentials has provided useful insight into the mechanisms of congenital QT prolongation. Abnormalities of the monophasic action potential were described by Bonatti and colleages.[10] These workers described "humps" arising from phase 3 of the action potential. These humps were regarded by others as representing early afterdepolarisations,[22] a phenomenon produced in vivo by administering caesium chloride to canine hearts.[26] In these studies ventricular arrhythmias with similar electrocardiographic characteristics to torsade de pointes were described which were initiated by early afterdepolarisations. Jackman and colleagues reported torsades de pointe arising in humans coincidentally with a hump on the endocardial monophasic action potential; and it has been suggested that early afterdepolarisations are responsible for the initiation of torsades de pointe in humans. In their illustration (fig 50,[22]), the initiating ventricular extrasystole has a configuration and axis suggesting an origin remote from the site of the monophasic action potential recording.[22] This was confirmed by the fact that the onset of the ventricular premature contraction preceded that of the right ventricular monophasic action potential. We too have noted this phenomenon (fig 2). Thus changes in local right ventricular monophasic action potential contour may be irrelevant to the onset of the premature extrasystole. Though we saw "humps" on the monophasic action potentials of patient 4, it is clear that spontaneous torsade de pointes were not consequent upon the "hump" on the right ventricular monophasic action potential (fig 2).

The available data do not seem to support the early afterdepolarisations hypothesis, but they

Figure 6 Right atrial monophasic action potential recordings during atrial pacing in patient 6.



are consistent with the theory, advanced by Han and colleagues, Kuo and colleagues, and Surawicz that dispersion of repolarisation is responsible for torsade de pointes in these patients.[27-30] When dispersion of repolarisation was assessed in patients with normal hearts the degree of monophasic action potential dispersion was up to 40 ms[12 13] and in patients with congenital QT prolongation it ranged from 100 to 270 ms.[10] None the less, existing animal models of arrhythmias dependent on increased dispersion of repolarisation have been produced by large temperature gradients,[29] or injections of large doses of contrast into coronary arteries,[31] conditions seldom encountered in clinical practice. Nor does the production of early afterdepolarisations by caesium chloride occur in practice. Clinical observations of patients with torsade de pointes do not necessarily provide the solution to the question of mechanism, because most observations can be explained by both mechanisms. At the present time, neither of the two proposed substrates has been conclusively shown to be the cause of torsade de pointes in humans.

In normal subjects, the monphasic action potential duration decreased linearly with decreasing pacing cycle lengths over a range of 800 to 350 ms.[32] This has also been shown in guinea pig[33] and canine[34] ventricles in vitro. It is of note that the decrease in monophasic action potential duration in our patients was more consistent than changes in QT adaptation. Because the T wave is considered to be the summation of phase 3 of the action potential of all individual myocardial fibres, a parallel can be expected between the duration of the ventricular monophasic action potential and that of the QT interval.[35] None the less, the precision of this relation is affected by individual variation in monphasic action potential duration as well as the precision of measurement of both functions, so it is difficult to interpret the discrepancy between these functions that was seen in two patients in our study. Furthermore, the monophasic action potential looks only at one site within the ventricular mass, whereas the QT interval is the summation of an infinite number and it is possible that if recordings were made from several sites, variability in monophasic action potential adaptation would be found, consistent with the abnormal QT changes. Unfortunately, the patient who had the least QT rate adaptation (case 2) did not have monophasic action potentials recorded.

β Adrenergic blocking agents have long been used to treat arrhythmias associated with prolongation of the QT interval and were shown to reduce mortality over a ten year period from 78% in untreated patients to 6% in treated patients.[36] Studies in which patients were given intravenous β blockade have not shown any significant change in QT interval,[37 38] although a tendency for the QTc value to shorten as the heart rate fell was noted. While our results did not show any overall change in QT interval during sinus rhythm after β blockade, there was considerable interpatient variability, with some patients showing a shortening of QT interval and some an increase. It is of interest that propranolol normalised the QT rate adaptation in the two patients with abnormal baseline adaptation (patients 1 and 2). The mechanism of this normalisation is unclear but may be due to a reduction in the dispersion of repolarisation or a suppressant effect on afterdepolarisations, which has been shown in vitro.[22]

It is not surprising, in view of the small change seen in the QT interval, that no change in MAP_{90} duration was noted in our patients after β blockade. This accords with the work of others who also found no change in MAP_{90} duration after intravenous metoprolol.[37] Others, however, found that long term treatment with atenolol or metoprolol increased the MAP_{90} duration by 12% in patients with coronary artery disease.[37 39]

There are some limitations in the present study with the evaluation of QT dynamics. Pacing for 10 seconds does not take into account hysteresis of the QT interval. We have previously shown that the decrease in QT interval with increasing pacing rate occurs in a bi-exponential form and takes approximately three minutes to complete 90% of its adaptation.[40] If steady state QT intervals were obtained, however, the study would either be excessively long or only a few heart rates could be assessed. The pacing protocol was the same in all patients and it is surprising that no abnormalities were seen in the other six patients. It is unlikely that the observed abnormalities in rate adaptation were artefactual or due to inaccuracies in the measurement of the QT interval. All measurements were made by two observers, although in patient 1 the alteration of a few measurements would result in reasonably linear rate adaptation. For clinical reasons not all patients completed the full protocol.

In summary, in this study of ventricular repolarisation (monophasic action potential duration, monophasic action potential configuration ("humps"), monophasic action potential dispersion, and monophasic action potential/QT rate adaptation) in the long QT syndrome no single abnormality could be identified as being associated with the tendency to develop torsade de pointes. The meaning of "humps" or early afterdepolarisation seen in vivo remains unclear; when such features were seen in our patients they seemed to be irrelevant to the onset of the arrhythmia. Abnormal rate adaptation was found in only a few patients and is therefore unlikely to be directly related to the genesis of arrhythmias. Perhaps this response is found in only the most severely affected cases. Dispersion of repolarisation has long been suggested as a potential mechanism for ventricular arrhythmias in this syndrome.[41] Our data, albeit limited, are not inconsistent with this suggestion but the mere presence of inhomogeneity of repolarisation during sinus rhythm cannot be adduced as evidence for the hypothesis. Our study has not clarified the role of differential sympathetic neural activity in this syndrome.[36] Other evidence indicates that it is likely to be of secondary importance to a primary cellular abnormality that continues to exist when sympathetic influences are removed.

We thank Dr E A Shinebourne for permission to include patients 2–5 in this study NJL is the holder of a Squibb Cardiovascular Research Fellowship.

1 Jervell A, Lange-Nielsen F. Congenital deaf mutism, prologned QT interval, and sudden death. *Am Heart J* 1957,54:59–68.

2 Romano C, Gemme G, Pongiglione R Aritmie cardiache rare dell'eta periatrica: II. Accessi sincopali per fibrillazione ventricolare parossistica *Clin Pediatr (Bologna)* 1963,45:656–61

3 Ward OC. New familial cardiac syndrome in children. *J Ir Med Assoc* 1964,54:103–6.

4 Attwell D, Lee JA. A cellular basis for the primary long Q-T syndromes. *Lancet* 1988;i.1136–9 .

5 Cowan JC, Yusoff K, Moore M, *et al.* Importance of lead selection in QT interval measurement. *Am J Cardiol* 1988,61:83–7.

6 Day CP, McComb JM, Campbell RWF. QT dispersion an indication of arrhythmia risk in patients with long QT intervals. *Br Heart J* 1990;63:342–4.

7 Taran LM, Szilagyi N. The duration of the electrical systole (QT) in acute rheumatic carditis in children *Am Heart J* 1947;33:14–26

8 Bazett HC. An analysis of the time relationships of the heart. *Heart* 1920;7:353–70.

9 Ward DE. Prolongation of the QT interval as an indicator of risk of a cardiac event. *Eur Heart J* 1988,9(suppl G): 139–44.

10 Bonatti V, Rolli A, Botti G. Recording of monophasic action potentials of the right ventricle in long QT syndromes complicated by severe ventricular arrhythmias *Eur Heart J* 1983;4·168–79.

11 Brorson L, Olsson SB. Right atrial monophasic action potential in healthy males. *Acta Med Scand* 1976,199· 433–46.

12 Hoffman BF, Cranefield PF, Lepeschkin E, Surawicz B, Herrlich HC. Comparison of cardiac monophasic action potentials recorded by intracellular and suction electrodes. *Am J Physiol* 1959;196 1297–301.

13 Franz MR, Bargheer K, Rafflenbeul W, Haverich A, Lichtlen P. Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence of the genesis of the T wave. *Circulation* 1987;75:379–86.

14 Rickards AF, Norman J. Relation between QT interval and heart rate: new design of physiologically adaptive cardiac pacemaker. *Br Heart J* 1981;45.56–61.

15 Horstmann E, Koenn B. Temporal relationship between exercise and QT shortening in patients with QT. pacemakers. *PACE* 1989;12 1080–4.

16 Lecocq B, Lecocq V, Jaillon P. Physiologic relation between cardiac cycle length and QT duration in healthy volunteers. *Am J Cardiol* 1989;63:481–6.

17 Romano M, Clarizia M, Onofrio E, *et al.* Heart rate, PR, and QT intervals in normal children: a 24-hour Holter monitoring study. *Clin Cardiol* 1988;11·839–42.

18 Milne JR, Camm AJ, Ward DE, Spurrell RAJ. Effect of intravenous propranolol on QT interval. A new method of assessment. *Br Heart J* 1980;43:1–6.

19 Milne JR, Ward DE, Spurrell RAJ, Camm AJ. The ventricular paced QT interval—the effects of rate and exercise *PACE* 1982,5:352–8.

20 Susmano A, Graettinger JS, Carleton RA. The relationship between Q-T interval and heart rate. *J Electrocardiol* 1969;2·269–74

21 Akhras F, Richards AF. The relationship between QT interval and heart rate during physiological exercise and pacing *Jpn Heart J* 1981,22.345–51.

22 Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, Lazarra R The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis* 1988;31·115–72.

23 Wellens HJJ, Vermuelen A, Durrer D. Ventricular fibrillation occurring on arousal from sleep by auditory stimuli. *Circulation* 1972,46.661–5.

24 Phillips J, Ichinose H. Clinical and pathologic studies in the hereditary syndrome of a long QT interval, syncopal spells, and sudden death. *Chest* 1970;588:236–43.

25 Mitsutake A, Takashita A, Kuroiwa A, Nakamura M. Usefulness of the Valsalva maneuver in management of the long QT syndrome. *Circulation* 1981;63:1029–35

26 Levine JH, Spear JF, Guarnieri T, *et al* Cesium chloride-induced long QT syndrome. demonstration of afterdepolarizations and triggered activity in vivo. *Circulation* 1985;72:1092–103.

27 Han J, Goel BG. Electrophysiologic precursors of ventricular tachyarrhythmias. *Arch Intern Med* 1972, 192·749–55.

28 Han J, Moe GK. Nonuniform recovery of excitability in ventricular muscle. *Circ Res* 1964;14·44–60.

29 Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations *Circulation* 1983;67·1356–67.

30 Surawicz B Electrophysiologic substrate of torsade de pointes. dispersion of repolarization of early afterdepolarizations? *J Am Coll Cardiol* 1989;14·172–84.

31 Murdock DK, Euler DE, Becker DM, Murdock JD, Scanlon PJ, Gunnar RM Ventricular fibrillation during coronary angioplasty· an analysis of mechanisms. *Am Heart J* 1985;109:265–73.

32 Franz MR, Swerdlow CD, Liem B, Schaefer J Cycle length dependence of human action potential duration in vivo. Effect of single extrastimuli, sudden sustained rate acceleration and deceleration, and different steady-state frequencies. *J Clin Invest* 1988;82 972–9.

33 Savigny LV, Hohnloser S, Antoni H Effects of changes in frequency on guinea pig ventricular action potential duration and on QT interval under different experimental conditions. *Basic Res Cardiol* 1981;76·276–88

34 Moore EN, Preston JB, Moe GK Durations of transmembrane action potentials and functional refractory periods of canine false tendon and ventricular myocardium Comparisons in single fibres. *Circ Res* 1965,27·259–73

35 Olsson SB, Brorson L, Edvardsson N, Varnauskas E. Estimation of ventricular repolarization in man by monophasic action potential recording technique. *Eur Heart J* 1985,6(suppl D):71–9

36 Schwartz PJ, Locati E. The idiopathic long QT syndrome pathogenetic mechanisms and therapy. *Eur Heart J* 1985,6(suppl D) 103–14

37 Edvardsson N, Olsson SB. Effects of acute and chronic beta-receptor blockade on ventricular repolarisation in man. *Br Heart J* 1981;45:628–36

38 Creamer JE, Nathan AW, Shennan A, Camm AJ. Acute and chronic effects of sotalol and propranolol on ventricular repolarisation using constant-rate pacing *Am J Cardiol* 1986;57:1092–6.

39 Way BPJ, Forfar JC, Cobbe SM. Comparison of the effects of chronic oral therapy with atenolol and sotalol on ventricular monophasic action potential duration and effective refractory period *Am Heart J* 1988,116.740–6

40 Lau CP, Freedman AR, Fleming S, Malik M, Camm AJ, Ward DE. Hysteresis of the ventricular paced QT interval in response to abrupt changes in pacing rate. *Cardiovasc Res* 1988,22:67–72.

41 Surawicz B, Knoebel SB Long QT· good bad or indifferent. *J Am Coll Cardiol* 1984;4:398–413

Br Heart J 1991;66:238–43

Influence of colour Doppler echocardiography on the ultrasonic assessment of congenital heart disease: a prospective study

J P Gnanapragasam, A B Houston, W B Doig, R Fraser, S Lilley, E Murtagh, G Olafsson

Abstract

***Objective*—To evaluate the additional information provided by colour Doppler in the ultrasonic assessment of congenital heart disease.**

***Patients and methods*—A prospective study of 215 children (age range 1 day–16 years) presenting with clinical signs of congenital heart disease.**

***Results*—Colour Doppler was essential for the diagnosis of an anomalous left coronary artery and altered the management of a patient initially diagnosed as having cardiomyopathy. Colour Doppler provided extra information, but without major impact on management, in the following: the diagnosis of ventricular septal defects associated with other defects, of multiple ventricular septal defects, of anomalous pulmonary venous drainage, and of mild mitral regurgitation; the demonstration of site of coarctation, of stenotic or hypoplastic pulmonary artery branches, of unobstructed flow through a right atrial membrane, and of left ventricle to right atrium regurgitation; the assessment of the width of the duct and of flow through the patent foramen ovale in transposition and tricuspid atresia; the differentiation of pulmonary atresia from critical pulmonary stenosis and the measurement of maximum velocity of tricuspid regurgitation.**

***Conclusions*—Ideally all patients should undergo colour Doppler studies before cardiac surgery to ensure a more accurate diagnosis. However, since the additional information provided does not affect the management in most patients, machines without colour Doppler can provide a satisfactory service in paediatric cardiology centres in countries where resources are limited.**

Department of Cardiology, Royal Hospital for Sick Children, Glasgow
J P Gnanapragasam
A B Houston
W B Doig
R Fraser
S Lilley
E Murtagh
G Olafsson

Correspondence to
Dr J P Gnanapragasam,
Department of Cardiology,
Royal Hospital for Sick
Children, Glasgow G3 8SJ.

Accepted for publication
11 April 1991

Cross sectional imaging of cardiac structures[1] and spectral Doppler examination of cardiac flow patterns[2] can provide an accurate assessment of most congenital cardiac defects. While spectral pulsed wave Doppler displays the velocity of only a single sample volume, colour Doppler provides a graphic display of flow velocity profiles superimposed over an area of the cross sectional image. Because this can facilitate the recognition of abnormal flow and of correlation with the underlying structural abnormality the use of colour coded Doppler velocity mapping should increase the diagnostic potential of cardiac ultrasound.[3] However, there have been no prospective studies to ascertain the influence of colour Doppler on the final non-invasive assessment of congenital heart disease. This information would be very useful in centres where some studies are still performed on machines without colour Doppler and is particularly relevant in the current period of worldwide expansion in paediatric cardiology for centres with limited financial resources. Knowledge of the capabilities and limitations of the techniques is important because most infants and children with congenital heart disease are now referred for surgery on the basis of non-invasive investigations.[4 5] We therefore carried out a prospective study to assess the additional information provided by colour Doppler in the non-invasive assessment of congenital heart disease.

Patients and methods

PATIENTS

We studied 215 patients (age range 1 day to 16 years) presenting with clinical signs of congenital heart disease. There were 84 neonates, 54 older infants, and 77 older children. The patients were studied at initial presentation and their diagnoses are listed in the table. In order to perform a detailed ultrasound examination on patients enrolled in the study without disrupting the work of the department some new patients could not be enrolled in the study during busy clinic sessions. Patients were excluded purely because machine time was not available and not on the basis of medical criteria.

METHODS

The studies were performed by a doctor or an experienced technician who was aware of the provisional diagnosis. A detailed cross sectional study was performed first. This was followed by Doppler interrogation with non-image linked (stand alone) continuous wave Doppler and image linked (duplex) continuous and pulsed wave Doppler. When the operator was satisfied that all possible information had been obtained with each technique the findings were recorded in detail. Colour Doppler examination was then carried out and the additional information obtained by this

List of diagnoses with the total number of defects in patients, number who were catheterised before surgery or during interventional procedures, and number treated by palliative or corrective surgery

Diagnosis	*Total*	*Catheterised*	*Operated*
Ventricular septal defect:			
Single isolated	51	1	2
Single with other defect	49	—	—
Multiple	6	0	0
Patent ductus arteriosus			
Isolated	14	1*	3
With other defect	49	—	—
Atrial septal defect.			
Secundum	27	1	9
Sinus venosus	1	0	1
Atrioventricular septal defect	14	1	10
Pulmonary valve stenosis	11	2*	0
Subpulmonary stenosis	6	2	2
Pulmonary artery stenosis	4	2	2
Tetralogy of Fallot	10	3	4(1†)
Pulmonary atresia with VSD	3	0	3†
Pulmonary atresia with intact septum	4	0	4†
Double outlet right ventricle	11	1	9†
Aortic valve stenosis	11	0	1
Subaortic stenosis	4	0	3
Supra-aortic valve stenosis	1	0	1
Coarctation	17	1	17
Hypoplastic left heart	6	0	6
Transposition	11	0	11
Tricuspid atresia	3	0	3†
Double inlet ventricle	2	0	2†
Mitral regurgitation/stenosis	3	0	1
Anomalous left coronary artery	1	0	1
Dilated cardiomyopathy	3	0	0
Common arterial trunk	1	0	1
Common arterial trunk with IAA	1	0	0
Aortic origin of pulmonary artery	1	0	1
TAPVD	1	0	1
Cor triatriatum	1	0	1
Cor triatriatum dexter	1	0	1

*Interventional catheterisation. †Palliative surgery.
IAA, interrupted aortic arch; TAPVD, total anomalous pulmonary venous drainage; VSD, ventricular septal defect.

method was recorded. There was no time limit on the performance of the echocardiography study and the duration varied with the complexity of the lesion and the operator used each mode of examination for a variable period of time. The ultrasound examination was carried out with a Vingmed CFM 700 system with a 2 MHz continuous wave non-imaging transducer and a selection of 7·5, 5·0, 3·5 MHz combined imaging and Doppler transducers. Colour flow mapping was performed with or without variance and using the appropriate gain and filter settings. Frame by frame analysis of recalled images was used as required.

We used the identification of defects by colour Doppler as the reference standard for the diagnosis. It is possible that colour Doppler did not detect some defects which remained unidentified but this would not affect the aim of the study which was to determine the advantage of colour Doppler over conventional studies. Cardiac catheterisation, carried out preoperatively in 12 patients (to obtain information on coronary artery anatomy, distal pulmonary artery branch anatomy, or shunt data) and for interventional procedures in three patients (table), did not alter the diagnosis in any patient.

One of the apparent benefits of colour Doppler flow mapping is that it increases the certainty of a diagnosis. To make the study as objective as possible and to eliminate any possible bias we confined our study to the finding of additional information and did not assess the role of colour Doppler in strengthening previously available information. We studied patients only at the initial examination, and the role of colour Doppler in the postoperative evaluation of patients was not assessed.

Results

To simplify reporting of the assessment of the results we considered the findings under the diagnostic categories determined by the final non-invasive diagnosis. The total number of defects analysed exceeded the number of patients in the study because many patients had more than one defect.

VENTRICULAR SEPTAL DEFECT (n = 106)

Single isolated ventricular septal defects (n = 51)

Defect localisation—The presence of flow through a ventricular septal defect, but not its site, was shown in all 51 cases by the non-imaging continuous wave transducer. Cross sectional echocardiography successfully showed the site of a defect in only 28 of the 51 patients with a single uncomplicated lesion, including two in whom the defect appeared to be closed by tricuspid valve tissue. However, image linked high pulse repetition frequency Doppler echocardiography identified the approximate site of the ventricular septal defect in 18 of the 23 patients in whom the defect could not be seen on imaging, and colour Doppler showed the exact site of defect in all 23 patients. The five defects whose site could be located only with the use of colour Doppler were very small and situated in the trabecular (n = 2) and apical (n = 3) muscular septum. In the two patients with apparent closure of a perimembranous ventricular septal defect by tricuspid valve tissue colour Doppler showed the site of flow through the aneurysm.

Estimation of right ventricular pressure—The pressure drop across the ventricular septal defect estimated by aligning the Doppler beam along the direction of the colour jet was more than 10 mm Hg greater than that estimated without colour Doppler in only two patients (85–96 mm Hg, 40–52 mm Hg). The spectral signal of tricuspid regurgitation was sought in every patient and a satisfactory signal showing the peak velocity from which the right ventricular pressure could be estimated was obtained in 17 of the 51 patients. The use of colour Doppler to localise the flow of tricuspid regurgitation improved the spectral waveforms and enabled the maximum velocity to be measured in four additional patients.

Single ventricular septal defect with other defects (n = 49)

This group had ventricular septal defects associated with other defects but not atrioventricular septal defects which are considered separately. The presence of a ventricular septal defect was detected without the use of colour Doppler in 44 patients. The remaining five had very small muscular defects the presence of which was unsuspected until colour Doppler was used (pulmonary stenosis 3, transposition 1, coarctation 1).

Multiple ventricular septal defect (n = 6)
Colour Doppler identified two areas of flow through the ventricular septum in six patients. Cross sectional imaging showed both defects in only two patients. Spectral Doppler detected a signal of ventricular septal defect flow in all patients, but in four patients the presence of more than one defect was not recognised until colour Doppler was used.

ATRIAL SEPTAL DEFECT (n = 28)

There were 27 patients with a secundum atrial septal defect, two of which were fenestrated defects, and one patient with a sinus venosus defect. Imaging studies showed the defect in the atrial septum in every patient and the anomalous site of entry of the right lower pulmonary vein in the patient with an inferior sinus venosus defect. However, in another child with a secundum defect, anomalous drainage of the right pulmonary veins into the inferior vena cava was unsuspected until colour Doppler echocardiography showed an unusual flow signal entering the inferior vena cava near its junction with the right atrium.

We obtained a complete spectral signal of tricuspid regurgitation that enabled its maximum velocity to be measured in 10 patients without the use of colour Doppler; in one additional patient the maximum velocity was measured by using colour.

ATRIOVENTRICULAR SEPTAL DEFECT (n = 14)

Cross sectional imaging clearly showed the atrial component of the defect in all patients and a ventricular septal defect in 11 patients. Colour Doppler showed a very small ventricular septal defect at the crest of the septum in an additional patient. This ventricular septal defect could not be detected by spectral Doppler because the flow signal was obscured by atrioventricular valve regurgitation which arose from the central part of the valve. Cross sectional imaging showed a common valve in five patients and two separate valve components in nine. Spectral Doppler detected atrioventricular valve regurgitant flow on the left side in 13 patients and on the right side in 10, and left ventricle to right atrium regurgitant flow was suspected on duplex Doppler in one patient. This was confirmed by colour Doppler, which also showed similar left ventricle to right atrium flow in six other patients.

PULMONARY STENOSIS AND TETRALOGY OF FALLOT (n = 31)

Colour Doppler provided information on pulmonary artery branch anatomy in five patients in whom this was not obtained by imaging owing to obscuring by lungs. It defined the size of a very hypoplastic left pulmonary artery (n = 1) and showed normal sized distal pulmonary artery branches (n = 2) in patients with tetralogy of Fallot. In a patient with isolated distal left pulmonary artery stenosis colour Doppler showed the site of narrowing which could not be seen on imaging. In another patient with normal sized right and left central pulmonary arteries colour Doppler showed areas of turbulence more peripherally in the lungs, indicating the presence of peripheral pulmonary artery stenoses.

A neonate with double outlet right ventricle and narrowing of the right ventricular outflow tract had a very dysplastic pulmonary valve that seemed to have a small orifice, but flow through it was difficult to demonstrate by duplex Doppler owing to interference by flow from a large duct. Colour Doppler showed an area of flow through the tiny orifice of the valve that was distinct from the ductal jet into the pulmonary artery.

Colour Doppler did not provide any additional information in the other patients in terms of defining the anatomy or estimating the maximum velocity across the stenosis.

PULMONARY ATRESIA WITH AND WITHOUT VENTRICULAR SEPTAL DEFECT (n = 7)

Colour Doppler had no influence on the detection of confluence of pulmonary artery branches, presence of a main pulmonary artery, or on the measurement of proximal pulmonary artery branch size. In two patients the pulmonary artery branches were seen more distally with the use of colour Doppler. Pulmonary valve atresia was diagnosed by imaging in all patients except one in whom it could not be distinguished from critical pulmonary stenosis, even with the use of duplex Doppler. Colour Doppler established the diagnosis in this patient by showing no flow across the valve. Colour Doppler showed multiple areas of low velocity flow in the right ventricular myocardium and showed myocardial sinusoids in a patient.

LEFT VENTRICULAR OUTFLOW OBSTRUCTION (n = 15)

The site of obstruction was identified without the use of colour Doppler in all patients and the maximum gradient was best obtained by non-imaging continuous wave Doppler. The spectral signal of mild aortic regurgitation was noted in five patients (three subaortic stenosis and two aortic stenosis) and colour Doppler identified a very small flow area of trivial aortic regurgitation in four other patients (one subaortic stenosis and three aortic stenosis).

HYPOPLASTIC LEFT HEART SYNDROME (n = 6)

Colour Doppler did not influence the detection of mitral atresia (n = 4) or aortic atresia (n = 5). In one patient an extremely thin aortic arch was identified only when colour Doppler showed retrograde flow within it. These findings were confirmed at necropsy.

COARCTATION OF THE AORTA (n = 17)

Continuous wave Doppler showed a coarctation type signal from the proximal descending aorta in all patients. The site of narrowing in the descending aorta was identified on imaging in 13 patients. In the other four the images of the descending aorta were inadequate to pinpoint the area of narrowing. Demonstration of proximal acceleration and a narrower area of turbulence or variance by colour Doppler identified the site of coarctation in all patients. The three main branches arising from the arch were seen on imaging in every patient and the coarctation was noted to be proximal to the origin of the left subclavian artery in one patient.

TRANSPOSITION OF THE GREAT ARTERIES ($n = 11$)
Transposition of the great arteries was diagnosed by imaging in all patients. No patient had a clear defect in the atrial septum but duplex Doppler detected flow through the patent foramen ovale in all patients. Colour Doppler outlined the width of the area of flow through the atrial septum, which gave an indication of mixing between the two circulations.

ARTERIAL DUCTS ($n = 63$)
A duct was detected without colour Doppler in 62 patients. In the other patient colour Doppler showed a tiny area of continuous flow into the main pulmonary artery and showed a previously undetected duct.

Twenty nine of these 63 patients had a duct dependent pulmonary or systemic circulation; in two of them the duct was not visible on imaging, though ductal flow was detected by spectral Doppler. In these patients colour Doppler outlined the area of flow within the narrow ductal lumen and enabled assessment of the width of the duct.

MITRAL REGURGITATION ($n = 3$)
Colour Doppler was not of additional value in a patient with mild mitral regurgitation associated with mitral valve prolapse and in a patient with severe rheumatic mitral regurgitation and stenosis. In the third patient in whom a ventricular septal defect was suspected on clinical examination, a high velocity systolic spectral signal flowing away from the transducer was misinterpreted as flow through an apical ventricular septal defect. The mitral valve was structurally normal and no ventricular septal defect was seen on imaging. Because colour Doppler showed a small flow jet of mitral regurgitation but no ventricular septal defect we made an unsuspected diagnosis.

OTHER DEFECTS
The diagnosis of an anomalous left coronary artery was considered in a neonate with poor left ventricular function but both coronary arteries appeared to arise from the aorta and there were no other imaging features associated with the lesion. Colour Doppler was essential for reaching the diagnosis by showing retrograde flow in the left coronary artery and flow into the inferomedial aspect of the main pulmonary artery. Colour Doppler also allowed firm exclusion of this diagnosis in three other infants with dilated cardiomyopathy.

In a patient with a right atrial membrane (cor triatriatum dexter) the large membrane prolapsing into the tricuspid valve orifice was clearly seen on imaging but it was difficult to exclude obstruction with certainty when we used duplex Doppler. Colour Doppler examination in multiple planes confirmed unobstructed flow over the sides of this membrane.

Tricuspid atresia was diagnosed and associated defects assessed in three patients without the use of colour Doppler, which was useful only in outlining the area of flow through an aneurysmal patent foramen ovale in one patient. The other two patients had clear gaps in the atrial septum.

Colour Doppler did not provide any additional information in the assessment of patients with the following defects: common arterial trunk, interrupted aortic arch with a common arterial trunk, anomalous origin of the right pulmonary artery from the aorta, criss-cross arrangement of the atrioventricular valves associated with double outlet right ventricle, cor triatriatum with an obstructed orifice, situs inversus with dextrocardia, unobstructed supracardiac total anomalous pulmonary venous drainage, double inlet left ventricle.

Discussion

The demonstration of a moving cross sectional image superimposed with real time flow data colour coded for velocity and direction is visually pleasing and enables an easier and faster cardiac ultrasound examination.[6 7] This study has not addressed these aspects but has determined the ultrasound information that may be missed if colour Doppler is not used.

In our series of 215 patients colour Doppler was essential for establishing the primary diagnosis in only two patients. The use of colour Doppler[8] altered the diagnosis from cardiomyopathy to anomalous origin of the left coronary artery and made a very important change in the management of the patient. A patient with minor mitral regurgitation was misdiagnosed as having a probable apical ventricular septal defect on spectral Doppler. (A similar spectral signal of flow away from the transducer was obtained in two other patients in whom colour Doppler confirmed an apical ventricular septal defect.) Review of the echocardiogram suggests that it is likely that the correct diagnosis would have been made if the echocardiographer had not been biased by the provisional diagnosis. Since in practice most echocardiographic examinations are carried out in a goal orientated approach with the clinical diagnosis in mind, colour Doppler may be helpful in highlighting unsuspected defects.

Colour Doppler showed an additional abnormality in several cases in our study. Clinically the most significant of these was the detection of partial anomalous pulmonary venous drainage associated with an atrial septal defect. However, even if this had not been detected and the patient had undergone surgery without cardiac catheterisation the anomalous veins would have been detected and dealt with at operation. As it is often not possible to identify all four pulmonary veins on imaging even in infants with normal pulmonary venous drainage,[9] cross sectional echocardiography cannot be relied upon to exclude partial anomalous pulmonary venous drainage.

Several studies have compared the sensitivity of colour Doppler with angiography in detecting small or multiple ventricular septal defects.[10–12] In our study none of the ventricular septal defects visible only with the use of colour Doppler merited further investigations or surgery. Four of these patients underwent surgery or interventional catheterisation for associated lesions (transposition, coarctation, subpulmonary stenosis, pulmonary valve stenosis) without closure of the ventricular septal defect.

Colour Doppler can be useful in the assessment of atrial septal defects in adults[13] but in children the defect is usually clearly seen on imaging. However, in the absence of a clear atrial septal defect, colour Doppler is useful in showing the width of the flow area through the septum in patients with cyanotic heart defects who are dependent on atrial shunting.

The assessment of severity of valve regurgitation by colour Doppler is a contentious issue because the extent of the colour jet is much more dependent on the driving pressure of regurgitation than on its volume.[14] The simultaneous display of the spatial orientation of different jets is nevertheless useful in detecting the presence of left ventricle to right atrium regurgitation in atrioventricular septal defects. Colour Doppler is extremely sensitive in detecting valve regurgitation[15] and the detection of trivial aortic regurgitation in four additional patients with aortic or subaortic stenosis was of no clinical importance. Localisation of the jet of tricuspid regurgitation by colour Doppler, however, can sometimes improve the spectral Doppler waveform enabling right ventricular pressure estimation.

Although the proximal parts of the right and left pulmonary arteries are seen on imaging, the distal parts are more difficult to visualise because they are often obscured by lungs. In our series colour Doppler enabled visualisation of normal sized distal right and left pulmonary arteries (n = 4), a stenotic distal pulmonary artery (n = 1), a hypoplastic pulmonary artery (n = 1), and bilateral peripheral pulmonary stenosis (n = 1). The impact of improved definition with colour Doppler echocardiographic examination of distal pulmonary artery branch anatomy in tetralogy of Fallot may be less important in clinical practice because in most centres all patients with tetralogy of Fallot undergo cardiac catheterisation before total repair.

In a recent comparative study of colour Doppler and angiography in the assessment of pulmonary atresia with ventricular septal defect Smyllie *et al* concluded that colour Doppler could be used reliably to assess patients with confluent pulmonary arteries and a unifocal blood supply.[16] In our series colour Doppler was useful in distinguishing pulmonary valve atresia from critical pulmonary stenosis in two infants. In critical pulmonary stenosis the tiny orifice in the dysplastic pulmonary valve may not be clearly visible on imaging[17] and with spectral Doppler flow through it may be difficult to distinguish from ductal flow. This differentiation could be useful because pulmonary valvotomy may be contemplated in addition to a shunt procedure.

The presence of a coarctation can be readily detected by continuous wave Doppler but it is not always possible to image the site of narrowing because the descending aorta may be obscured by lungs. Colour Doppler can show the precise site of narrowing in these patients, which may not be relevant to the method of surgical repair but nevertheless may reduce the need for cardiac catheterisation in cases of doubt.

Although it has been reported that colour Doppler facilitates maximum velocity measurement in valve stenosis by enabling optimum alignment of the Doppler beam,[18] in our series colour Doppler did not show a higher gradient in any patient with left or right ventricular outflow obstruction or coarctation. Colour Doppler merely shows the component of a jet in a two dimensional plane, and because it is not possible to predict the true direction of the jet the maximum velocity is best obtained by Doppler examination from several sites at varying angles.

It is difficult to be totally objective in the analysis of a comparative study of ultrasound methods because echocardiography is largely an interpretative process involving operator interaction. Hence the apparent deficiency of a technique to elucidate a diagnosis may lie in the operator's inability to assimilate and interpret the available information. This was apparent in the case of mild mitral regurgitation which was misdiagnosed as apical ventricular septal defect and also in a case of left heart hypoplasia in which a very thin aorta was identified only by using colour Doppler during the study but was clearly visible on imaging to another operator at a subsequent examination.

CLINICAL IMPLICATIONS

Our study shows that most patients with congenital heart disease can be diagnosed by imaging and duplex Doppler echocardiography with colour Doppler providing little additional information. The use of colour Doppler ensured appropriate surgical treatment for a patient with an anomalous coronary artery and led to preoperative cardiac catheterisation in a patient with anomalous pulmonary venous drainage. Although colour Doppler influenced the final non-invasive diagnosis in several other patients by providing further information on the diagnosis or by showing an additional defect it did not alter the course of conservative or surgical management of these patients. Such information is nevertheless important because it increases confidence in referring patients for surgery without invasive investigations. Ideally all patients should undergo a colour Doppler study before cardiac surgery because there is a very small but unavoidable risk of missing an important defect. Colour Doppler studies must also be performed on all patients with dilated cardiomyopathy of uncertain origin including those diagnosed in the past before colour Doppler became available.

We recommend that all centres undertaking major paediatric cardiac surgery should have the facility for colour Doppler studies. In paediatric cardiology centres in countries with limited financial resources, however, machines without colour Doppler can provide an adequate service because colour Doppler does not alter the management of most patients with congenital cardiac defects. Machines without colour Doppler are also quite adequate for the assessment of congenital heart defects in district hospitals with regular paediatric cardiology clinics and in neonatal units.

JPG is in receipt of a grant from the Equipment Evaluation Committee of the Scottish Home and Health Department.

1 Gutgesell HP, Huhta JC, Latson LA, Huffines D, McNamara D. Accuracy of two-dimensional echocardiography in the diagnosis of congenital heart disease. *Am J Cardiol* 1985;55 514–8.

2 Leung MP, Mok CK, Lau KC, Lo R, Yeung CY. The role of cross sectional echocardiography and pulsed Doppler ultrasound in the management of neonates in whom congenital heart disease is suspected. a prospective study. *Br Heart J* 1986;56:73–82.

3 Miyatake K, Okamoto M, Kinoshita N, *et al.* Clinical applications of a new type of real-time two-dimensional Doppler flow imaging system. *Am J Cardiol* 1984;54 857–68

4 Huhta JC, Glasow P, Murphy DJ, *et al.* Surgery without catheterization for congenital heart defects· management of 100 patients *J Am Coll Cardiol* 1987;9:823–9.

5 Leung MP, Cheung DLC, Lo RNS, Mok CK, Lee J, Yeung CY. The management of symptomatic neonates with suspected congenital heart disease using combined cross-sectional echocardiography and pulsed Doppler flow study as the definitive investigations. *Int J Cardiol* 1989;24 41–6.

6 Goldberg HJ. A perspective on color-coded Doppler echocardiography utility or just another pretty picture? *J Am Coll Cardiol* 1989,14:977–8.

7 Monaghan MJ, Mills P Doppler colour flow mapping technology in search of an application? *Br Heart J* 1989; 61:133–8.

8 Houston AB, Pollock JCS, Doig WB, *et al.* Anomalous origin of the left coronary artery from the pulmonary trunk: elucidation with colour Doppler flow mapping. *Br Heart J* 1990;63:50–4.

9 Sahn DJ, Allen HD, Lange LW, Goldberg SJ. Cross-sectional echocardiographic diagnosis of the sites of total anomalous pulmonary venous drainage. *Circulation* 1979, 60 1317–25

10 Sutherland GR, Smyllie JH, Ogilvie BC, Keeton BR Colour flow imaging in the diagnosis of multiple ventricular septal defects. *Br Heart J* 1989,62:43–9.

11 Chin AJ, Alboliras ET, Barber G, *et al* Prospective detection by Doppler color flow imaging of additional defects in infants with a large ventricular septal defect *J Am Coll Cardiol* 1990;15 1637–42.

12 Ortiz E, Robinson PJ, Deanfield JE, Franklin R, Macartney FJ, Wyse RKH. Localisation of ventricular septal defects by simultaneous display of superimposed colour Doppler and cross sectional echocardiographic images. *Br Heart J* 1985;54 53–60.

13 Suzuki Y, Kambara H, Kadota K, *et al.* Detection of intracardiac shunt flow in atrial septal defect using a real-time two-dimensional color-coded Doppler flow imaging system and comparison with contrast two-dimensional echocardiography *Am J Cardiol* 1985,56 347–50.

14 Simpson IA, Valdes-Cruz LM, Sahn DJ, Murillo A, Tamura T, Chung KJ Doppler color flow mapping of simulated in vitro jets: evaluation of the effects of orifice size and haemodynamic variables. *J Am Coll Cardiol* 1989,13: 1195–207

15 Yoshida K, Yoshikawa J, Shakudo M, *et al.* Colour Doppler evaluation of valvular regurgitation in normal subjects. *Circulation* 1988,78 840–7.

16 Smyllie JH, Sutherland GR, Keeton BR. The value of Doppler color flow mapping in determining pulmonary blood supply in infants with pulmonary atresia with ventricular septal defect. *J Am Coll Cardiol* 1989;14. 1759–65.

17 Silove ED, de Giovanni JV, Shiu MF, Yi MM Diagnosis of right ventricular outflow obstruction in infants by cross sectional echocardiography. *Br Heart J* 1983;50·416–20.

18 Pandian NG, Thanikachalam S, Elangovan D, Caldeira ME, Salem DN. Colour Doppler flow imaging in valvular stenosis. *Echocardiography* 1987;4·515–26.

Br Heart J 1991;66:244–5

CASE REPORTS

Conservative surgery in multiple cusp involvement in tricuspid valve endocarditis

J R Anderson, P Scott, R U Nair

Abstract

Tricuspid and mitral valve endocarditis caused by *Staphylococcus epidermidis* in a 57 year old previously healthy man with no history of drug abuse presented as bi-ventricular failure and multiple episodes of pulmonary emboli. He was treated for four weeks with intravenous antibiotics and had serial echocardiographic assessment of the vegetation on the tricuspid valve. This was followed by mitral valve replacement, local excision of vegetation from all the three cusps of the tricuspid valve, and autologous pericardial reconstruction of these cusps with functional assessment by perioperative transoesophageal echocardiography. Postoperative cardiac function was excellent and serial echocardiographic assessment confirmed satisfactory tricuspid valve function.

This is believed to be the first recorded case in which autologous pericardial repair was used to reconstruct all the three cusps in a tricuspid valve after excision of vegetations.

Bacterial endocarditis of the tricuspid valve accounts for only 5–10% of all cases of infective endocarditis.[1] The response to medical treatment is usually good but surgery is indicated when the condition is complicated by repeated pulmonary emboli or if the size of the vegetations increases or remains more than 1 cm on echocardiography.[2]

Case report

A 57 year old previously healthy man was admitted on 16 May 1990 with rigors, lassitude, and weight loss. He had had an acute upper respiratory tract infection in December 1989 and remained well until February 1990. Since then he had become unwell and had lost 13 kg. One month before admission he had been prescribed amoxycillin for a throat infection. There was no history of rheumatic fever or intravenous drug abuse.

At admission he was pyrexial (38·8°C) with a tender nodule on the pulp of his right middle finger. Auscultation revealed a grade III pansystolic murmur at the left sternal edge.

A precordial echocardiogram showed thickened mitral and tricuspid valve leaflets. This was confirmed by transoesophageal echocardiography which also showed vegetations >1 cm across on the septal and anterior tricuspid valve cusps. There was mild tricuspid and mitral reflux but left ventricular function was good.

Infective endocarditis was diagnosed and treatment with intravenous antibiotics started. *Staphylococcus epidermidis* was isolated from the blood but his pyrexia continued despite prolonged medical treatment.

At operation there was a large vegetation on each tricuspid valve cusp. Each vegetation was excised and the cusp was repaired with an autologous pericardial patch. A flexible Duran ring was inserted for additional support and perioperative transoesophageal echocardiography showed no regurgitation.

A large vegetation on the mitral valve was excised and repaired by direct suture with shortening of an elongated chordae. Unfortunately the valve was not competent and had to be replaced with a Medtronic (size 23) prosthesis. The cardiopulmonary bypass was discontinued easily.

Postoperatively, he made an excellent recovery with resolution of all symptoms. An echocardiogram obtained before discharge showed normal prosthetic mitral valve function with only mild residual tricuspid incompetence. Ten weeks after operation he was very well and no tricuspid regurgitation was seen on the echocardiogram.

Discussion

When surgery is indicated for endocarditis of the tricuspid valve, the options are (*a*) debridement with valve preservation, (*b*) valvectomy with prosthetic replacement, and (*c*) valvectomy without prosthetic replacement.

The mortality from tricuspid valve surgery is high but this may be owing to associated aortic and mitral valve disease and late presentation for surgery.[3] Earlier intervention before cardiac decompensation occurs may improve the results of surgery.

Valvectomy without prosthetic replacement is associated with troublesome postoperative right heart failure in some patients.[1] However, since this treatment for persistent right sided

Killingbeck Hospital, Leeds
J R Anderson
P Scott
R U Nair

Correspondence to
Mr R U Nair, FRCS,
Department of
Cardiothoracic Surgery,
Killingbeck Hospital, York
Road, Leeds LS14 6UQ.

endocarditis was reported,[4] more and more cases have been described where it was possible to preserve the tricuspid valve by careful removal of the vegetations.[5–7] The use of autologous pericardium for tricuspid valve repair has been described before but was used only if two minor leaflets or one major leaflet were involved.[8]

Our case was complicated by the associated endocarditis of the mitral valve where it was not possible to preserve the valve because of coexisting degenerative changes. Apart from this, the tricuspid valve also had vegetations in all three cusps and removal of these with part of the valve cusps resulted in three significant defects. Repair of these defects with autologous pericardium enabled us to maintain good apposition of the valve cusps. This was further reinforced with the insertion of a Duran ring.

In a large series of cases of tricuspid valve surgery, there was no difference in mortality between valve repair and valve replacement.[3] It is, however, our view that conservative surgery of the atrioventricular valve should be attempted when practical and possible. This case illustrates the feasibility of conserving the tricuspid valve despite the presence of vegetations on all the leaflets.

The excellent postoperative valve function after this repair is very encouraging but more cases are needed to establish that this should be attempted every time this clinical situation occurs.

1 Chan P, Ogilby JD, Segal B. Tricuspid valve endocarditis. *Am Heart J* 1989;**117**:1140–6.
2 Buda AJ, Zotz RJ, Le Mire MS, Bach DS. Prognostic significance of vegetations detected by two dimensional echocardiography in infective endocarditis. *Am Heart J* 1986;**112**:1291–6.
3 McGrath LB, Gonzales-Lavin L, Bailey BM, Grunkemeier GL, Fernandez JF, Laub GW. Tricuspid valve operations in 530 patients. *J Thorac Cardiovasc Surg* 1990;**99**:124–33.
4 Arbulu A, Thoms MW, Wilson RF. Valvulectomy without prosthetic replacement, a lifesaving operation for tricuspid pseudomonas endocarditis. *J Thorac Cardiovasc Surg* 1972;**64**:103–7.
5 Jagger JD, McGaughan BC, Pawsey CGK. Tricuspid valve endocarditis cured by excision of a single vegetation. *Am Heart J* 1986;**112**:626–7.
6 Chandraratna PA, Reagan RB, Imaizui T, Langevin E, Elkins RC. Infective endocarditis cured by resection of a tricuspid valve vegetation. *Ann Intern Med* 1978;**89**:517–8.
7 Tanaka M, Abe T, Hosokawa S, Suengaga Y, Hikosaka H. Tricuspid valve candida endocarditis cured by valve-sparing debridement. *Ann Thorac Surg* 1989;**48**:857–8.
8 Yee ES, Ullyott DJ. Reparative approach for right sided endocarditis. *J Thorac Cardiovasc Surg* 1988;**96**:133–40.

Comment

There are good reasons for Anderson *et al* to be proud of their technical achievement in repairing all three cusps of a tricuspid valve damaged by endocarditis. None the less, the question remains as to whether for the next patient they encounter this provides a better prospect than replacing the valve. Their view "that conservative surgery of the atrioventricular valve(s) should be attempted when practical and possible" reflects the current tide of opinion. However, in this instance, the attempt at repairing the mitral valve was abandoned because the surgeons regarded the attempted repair as unsatisfactory. The success they achieved vindicates their intraoperative decisions. The case emphasises that the excellent results reported for mitral valve repair include a selection process at this stage, and if bad intraoperative results had been accepted by the pioneers of mitral valve conservation it is likely that conservative operations on the mitral valve would have fallen into disrepute. In the case of the mitral valve there is a growing body of evidence to suggest that repair gives superior short and long term results for the patient. The ideal policy is much harder to establish in tricuspid valve operations because they are so relatively infrequent.[1] McGrath *et al* in a series of tricuspid valve operations in 530 cases were unable to demonstrate benefit for a conservative policy over the results achieved with valve replacement.[2] A recent report, also from Leeds, reports excellent long term results with a tissue valve tricuspid valve replacement in a series of 73 patients followed for, on average, nearly 10 years.[3] The evidence suggests that, although Anderson, Scott, and Nair achieved an excellent result by conserving the valve, a strategy aimed at replacing the valve with a reliable prosthesis might have done just as well. On the evidence available, an elaborate attempt to conserve a tricuspid valve in a patient with endocarditis who has to have mitral valve replacement to save his life seems hard to justify.

TOM TREASURE

St George's Hospital,
Blackshaw Road,
London SW17 0QT

1 Surgery for tricuspid regurgitation [editorial]. *Lancet* 1988;**ii**:1061–2.
2 McGrath LB, Gonzales-Lavin L, Bailey BM, Grunkemeier GL, Fernandez JF, Laub GW. Tricuspid valve operations in 530 patients. *J Thorac Cardiovasc Surg* 1990;**99**:124–33.
3 Eng J, Ravichandran PS, Kay PH, Murday AJ. Long-term results of Ionescu-Shiley valve in tricuspid position. *Ann Thorac Surg* 1990;**51**:200–3.

Br Heart J 1991;**66**:246–7

Double partitioning of the left atrium: a previously unreported echocardiographic finding in a case in which transoesophageal echocardiography aided operative resection

Frances A Bu'Lock, Paula Murphy, Robin P Martin

Abstract

Precordial echocardiography showed two membranes obstructing pulmonary venous return in the left atrium of a 9 month old infant. This anomaly has not previously been described; therefore transoesophageal echocardiography was performed at the time of surgery. This confirmed the anatomy and aided complete resection of both membranes. Even in small infants transoesophageal echocardiography can provide useful information about complex atrial malformations.

Department of Paediatric Cardiology, Bristol Royal Hospital for Sick Children
F A Bu'Lock
R P Martin

Department of Radiology, Bristol Royal Infirmary
P Murphy

Correspondence to
Dr Frances A Bu'Lock,
Department of Paediatric
Cardiology, Royal Hospital
for Sick Children, St
Michael's Hill, Bristol, Avon
BS2 8BJ.

Transoesophageal echocardiography (TOE) is gaining widespread acceptance as an adjunct to precordial echocardiography, particularly where there is diagnostic doubt and/or difficulty in imaging more posterior structures such as the left atrium. We describe a previously unreported variant of cor triatriatum presenting in infancy where TOE aided optimal surgical management.

Case report

A 9 month old boy presented with a short history of weight loss, increasing dyspnoea, and cough. Intermittent breathlessness had been noted throughout life but development was normal. Clinical examination showed mild tachypnoea with subcostal recession and normal peripheral pulses. The liver was enlarged 4 cm below the costal margin and there was clinical evidence of right ventricular hypertrophy. Auscultation revealed a soft midsystolic murmur at the left sternal edge, a loud pulmonary component to the second heart sound, and a third heart sound. Chest *x* ray showed cardiomegaly and pulmonary venous prominence.

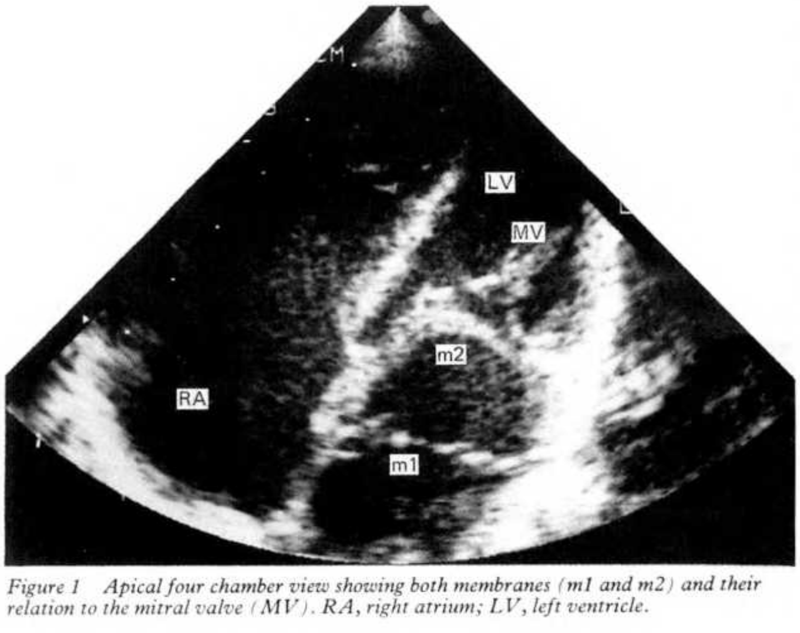


Figure 1 Apical four chamber view showing both membranes (m1 and m2) and their relation to the mitral valve (MV). RA, right atrium; LV, left ventricle.

Precordial echocardiography showed a dilated right atrium, ventricle, and pulmonary artery with right ventricular hypertrophy. There was tricuspid regurgitation with peak flow velocity on Doppler examination of 4·5 m/s; that was consistent with moderately severe right ventricular hypertension. The left atrium was partitioned in an unusual manner. The pulmonary veins connected to a proximal chamber that was separated from the mitral valve by two distinct membranes. The membranes had a common origin from the atrial septum at the level of the closed fossa ovalis. The proximal membrane (membrane 1) almost bisected the left atrium. The second more distal membrane (membrane 2) paralleled the aortic root proximally and was closely applied to (but separate from) the mitral valve more distally.

Both membranes ballooned towards the mitral valve in diastole, the distal one particularly giving the classic wind-sock appearance[1] of cor triatriatum (fig 1). Their relation to the left atrial appendage could not be clearly determined. The mitral valve apparatus was normal. Doppler examination showed two areas of flow through the distal atrium along the atrial septal and lateral aspects of membrane 2. Peak velocity was 2·3 m/s with continuous turbulent flow indicative of severe obstruction. No flow could be shown in the area between the two membranes.

Because of the unusual echocardiographic appearances, TOE examination was performed at the time of cardiac repair. A 5 MHz transoesophageal paediatric probe was used, connected to an Aloka SSD870 ultrasound system. The anatomy of the two membranes was confirmed and the left atrial appendage could be seen on the mitral side of the second membrane. There was spontaneous contrast within the proximal left atrium and between the membranes, which was indicative of stasis (fig 2).

During cardiopulmonary bypass, the left atrium was opened parallel to the inter-atrial groove. A large and "fairly redundant" dia-

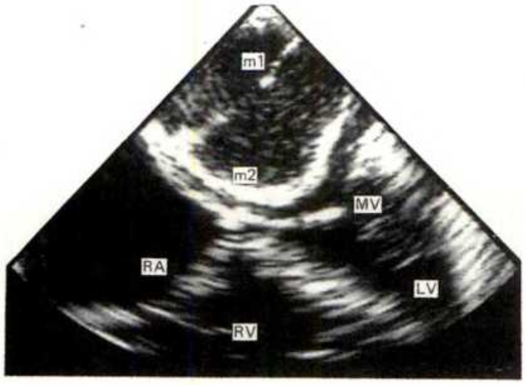


Figure 2
Transoesophageal four chamber image confirming the presence of two membranes (m1 and m2) and showing "spontaneous contrast" within the left atrium and between the two membranes. RA, right atrium; RV, right ventricle; LV, left ventricle; MV, mitral valve.

phragm was identified (membrane 1). A separate leaf of this diaphragm arose from its central region and the interatrial septum some distance from the main diaphragm (membrane 2). The anatomical details and route of blood flow were difficult to identify in situ; the clear preoperative visualisation of the anatomy proved most helpful. Complete excision of both membranes was verified intraoperatively with TOE and unobstructed pulmonary venous return was clearly demonstrated. Postoperative recovery was uneventful: the child was well and symptom free 12 months later.

Discussion

TOE is now feasible in all but the smallest infants,[2] though most congenital cardiac lesions can be adequately determined with precordial echocardiography. In our patient transoesophageal echocardiography gave useful confirmation of a previously undescribed left atrial anomaly in a small child. Magnetic resonance imaging has been advocated for confirmation of left atrial membranes[3,4] but is not always readily available. The use of TOE for diagnosis of cor triatriatum in adults has already been reported.[5,6] TOE may be valuable for atrial examination in small children. Intraoperative confirmation of the adequacy of membrane excision was also very helpful in this patient. Clarification of atrioventricular malformations[7] and assessment of pulmonary venous drainage anomalies may also be facilitated by the use of TOE.

We thank Dr S C Jordan and Mr J D Wisheart for permission to report their patient.

1 Östman-Smith I, Silverman NH, Oldershaw P, Lincoln C, Shinebourne EA. Cor triatriatum sinistrum. Diagnostic features on cross sectional echocardiography. *Br Heart J* 1984;**51**:211–9.
2 Stumper OFW, Elzenga NJ, Hess J, Sutherland GR. Transoesophageal echocardiography in children with congenital heart disease: an initial experience. *J Am Coll Cardiol* 1990;**16**:433–41.
3 Bissett GS, Kirks DR, Strife JL, Schwartz DC. Cor Triatriatum: diagnosis by MR imaging. *Am J Roentgenol* 1987;**149**:567–8.
4 Rumancik WM, Hernanz-Schulman M, Rutkowski MM, *et al*. Magnetic resonance imaging of cor triatriatum. *Pediatr Cardiol* 1988;**9**:149–51.
5 Schluter M, Langenstein BA, Thier W, *et al*. Transoesophageal two-dimensional echocardiography in the diagnosis of cor triatriatum in the adult. *J Am Coll Cardiol* 1983;**2**:1011–5.
6 Goldfarb A, Weinreb J, Daniel WG, Kronson J. A patient with right and left atrial membranes: the role of transoesophageal echocardiography and magnetic resonance imaging in diagnosis. *J Am Soc Echocardiogr* 1989;**2**:350–5.
7 Stumper OFW, Sreeram N, Elzenga NJ, Sutherland G. Diagnosis of atrial situs by transoesophageal echocardiography. *J Am Coll Cardiol* 1990;**16**:442–6.

Br Heart J 1991;66:248–9

Fatal rupture of an unsuspected post-traumatic aneurysm of the thoracic aorta during pregnancy

J N Townend, M K Davies, E L Jones

University of Birmingham Department of Cardiovascular Medicine, Queen Elizabeth Hospital, Birmingham
J N Townend
M K Davies

University of Birmingham Department of Pathology, Medical School, Birmingham
E L Jones

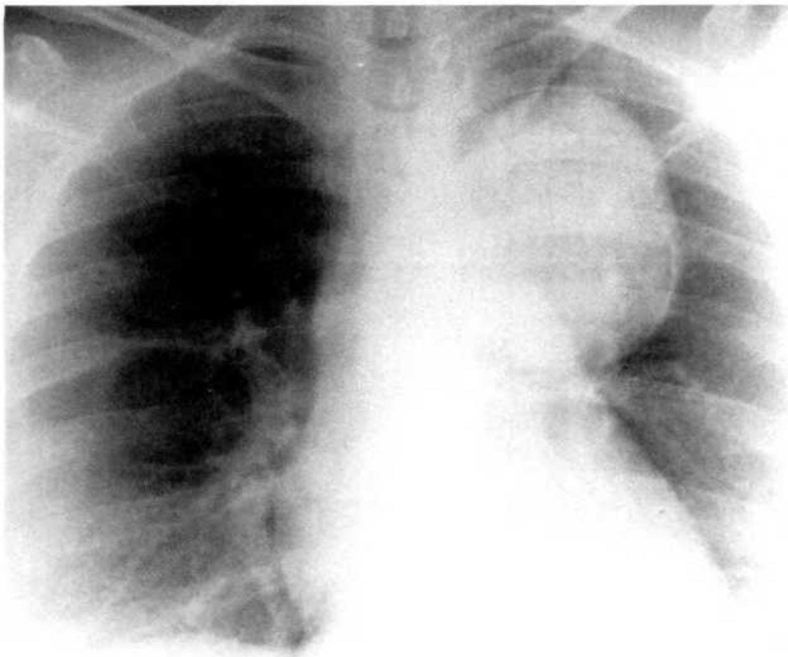
Correspondence to Dr J N Townend, Department of Cardiovascular Medicine, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH.

Abstract

A 27 year old woman presented during the third trimester of her second pregnancy complaining of chest pain. A chest radiograph showed a large aneurysm arising from the distal part of the aortic arch. She was transferred to the regional cardiothoracic centre but died suddenly on arrival. Necropsy confirmed a ruptured saccular aortic aneurysm arising just distal to the left subclavian artery. A history of a road traffic accident at the age of 12 was obtained from relatives after the patient's death.

Vascular and haemodynamic changes in pregnancy may have caused the rupture of this previously silent post-traumatic aortic aneurysm.

Rupture of arterial aneurysms is a rare complication of pregnancy.[1] Almost all of the reported cases of rupture of thoracic aortic aneurysms during pregnancy have been dissecting aneurysms; saccular aneurysms of the aortic arch are rare in young women and are usually secondary to systemic disease. We report a case of fatal rupture of a saccular thoracic aortic aneurysm during pregnancy in a previously fit young woman with no evidence of systemic disease. A history of previous trauma was obtained only after she died.



Chest radiograph showing a smooth rounded mass arising from the left upper mediastinum with calcification in the lateral aspect.

Case report

A 27 year old woman presented to her local hospital at 38 weeks' gestation in her second pregnancy complaining of chest and interscapular pain of 3 hours' duration. The pain had started suddenly during a visit to a supermarket and was associated with a "numb" sensation in the left arm. There was no prior history of chest pain or cardiopulmonary disease. Antenatal clinic visits had revealed mild hypertension at 34 weeks (blood pressure 140/96 mmHg) but otherwise the pregnancy had been uneventful. Routine serological testing for syphilis was negative. The first pregnancy two years earlier had also been complicated by mild hypertension; no chest radiograph was performed. She was obese and hypertensive with a blood pressure of 145/110 mm Hg but no other abnormality was detected. A chest radiograph (figure) showed a smooth rounded mass arising from the left upper mediastinum with calcification in the lateral aspect. The left costophrenic angle was clear. An unstable thoracic aortic aneurysm was diagnosed and the patient was transferred by ambulance to our hospital, a distance of nearly 60 miles. Immediately on arrival the patient collapsed with no pulse or spontaneous respiration: all efforts at resuscitation were unsuccessful. During the resuscitation procedure an emergency ceasarean section was performed but the infant was born with an Apgar score of zero and died several hours later.

A large left haemothorax was found at necropsy. The heart was normal as were the ascending aorta and the innominate, left common carotid, and left subclavian arteries. Immediately distal to the origin of the left subclavian artery there was a slight narrowing of the aorta distal to which there was a saccular aneurysm measuring 7 × 7 cm. The walls were very thin with foci of calcification and there was a posterior tear communicating with the left hemithorax. The rest of the aorta and arterial system was normal; there was no evidence of intimal fibrosis, medionecrosis, or dissection. Microscopy showed that the wall of the aneurysm was composed of thin layers of dense hyalinised fibrous tissue with foci of calcification and cholesterol crystal clefts consistent with old haemorrhage. The outer media and adventitia were intact. The aortic media at the constriction adjacent to the neck of the aneurysm showed fibrous disruption of the elastic lamellae consistent with an old traumatic laceration. Elsewhere the aortic wall was normal.

Relatives were subsequently asked about any history of injury. One recalled that at the age of 12 the patient had been a passenger in a car that overturned. She had been apparently unhurt and did not seek medical attention. It seems likely that a deceleration injury sustained then caused an aortic tear at the typical site and led to the development of a post-traumatic aneurysm.

Discussion

Sudden death owing to rupture of a post-traumatic aneurysm of the thoracic aorta during pregnancy has not been reported before. However, a case resembling this one was reported by Locufier *et al* in 1989.[2] They described a 22 year old woman in whom a saccular aortic aneurysm almost identical in position and size to our case was discovered on a "routine" chest radiograph performed the day after delivery. Pregnancy had been complicated by a pre-eclamptic episode but no other causative factor was identified. The aneurysm was successfully repaired.

Over 95% of traumatic aortic injuries involve the thoracic aorta and the usual site of laceration is 2 to 3 cm distal to the origin of the left subclavian artery. The adventitia can remain intact after the tearing of the inner layers of the aortic wall and this may lead to the development of a post-traumatic aneurysm. The inner margins of such aneurysms are formed of intimal fibrous strictures which may resemble a coarctation.[3] Only 2–5% of patients with aortic rupture survive long enough to develop a chronic aneurysm[4] and the natural history is that of progressive enlargement and eventual rupture. However, nearly one fifth of patients remain symptom free for over ten years after the causative injury.[5] It seems that in our patient rupture was precipitated by pregnancy and associated hypertension 15 years after the presumed injury.

Rupture of arterial aneurysms is a rare but recognised complication of pregnancy.[1] Changes in haemodynamic function (increases in blood pressure, stroke volume, and rate of pressure rise in systole) as well as in the structure of the media and intima of arterial walls[6 7] predispose to aneurysm formation and rupture. While intimal changes reverse after pregnancy those in the media do not, suggesting that multiparity may be a risk factor.[8] Dissecting aneurysms are by far the most common form of aortic aneurysm presenting during pregnancy[1] but saccular aneurysms have been described.[9]

Rupture of the cerebral, coronary, renal, ovarian, and in particular the splenic vessels during pregnancy have all been reported.[1] The third trimester is the most common time of rupture of aortic (and other) aneurysms in pregnancy with 75% of cases occurring in this period compared with 15% in the second trimester.[9] In most patients there seems to be no underlying cause other than pregnancy itself; previous trauma may be an unrecognised cause in an unknown proportion of patients. In an extensive historical review of aortic aneurysms presenting during pregnancy only one of 29 cases of aortic saccular aneurysms presenting during pregnancy was thought to be traumatic in origin; in 17 cases no aetiological factor other than pregnancy was identified.[9]

The chest radiograph has been abandoned as a screening investigation for women in early pregnancy. There may be a case for its selective use in patients with a history of serious trauma, however remote, but we are doubtful that such a history would have been forthcoming in this case. In the absence of any screening test, only a high index of suspicion leading to rapid diagnosis after presentation and prompt referral for surgery offer any hope in this life threatening complication of pregnancy.

JNT is a British Heart Foundation Junior Research Fellow

We thank Mr DER Bateman, Mr RS Bonser, and Dr RM Whittington, HM Coroner for Birmingham and Solihull Districts, for their permission to report this case

1 Barret JM, Hooydonk JE, Boehm FH Pregnancy-related rupture of arterial aneurysms *Obstet Gynecol Surv* 1982,37.557–66
2 Locufier JL, Bosschaerts T, Barthel J, Delwarte D, Barroy JP Aneurysm of the descending thoracic aorta in a young woman *J Cardiovasc Surg* 1989,30.499–502.
3 Kinley CE, Chandler BM. Traumatic aneurysm of thoracic aorta A case presenting as coarctation *Can Med Assoc J* 1967,96·279–81
4 Parmley LF, Mattingly TW, Manion WC, Jahnke EJ Non-penetrating traumatic injury of the aorta *Circulation* 1958;17·1086–101.
5 Bennet DE, Cherry JK. The natural history of traumatic aneurysms of the aorta *Surgery* 1967,61 516–23
6 Manalo-Estrella P, Barker AE. Histopathological findings in human aortic media associated with pregnancy *Arch Pathol* 1967,83:336–41
7 Schwarz OH, Hawker WD. Hyperplasia and hypertension of uterine vessels during various stages of pregnancy. *Am J Obstet Gynecol* 1950;60 967–74
8 Wexler BC Vascular degenerative changes in the uterine arteries and veins of multiparous rats *Am J Obstet Gynecol* 1970;107 6–16
9 Pedowitz P, Perell A Aneurysms complicated by pregnancy *Am J Obstet Gynecol* 1957,73:720–35.

BRITISH CARDIOLOGY

British Heart Foundation surveys (1987 and 1989) of United Kingdom treatment policies for acute myocardial infarction

Rory Collins, Desmond Julian

Clinical Trial Service Unit and Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford
R Collins

British Heart Foundation, London
D Julian

Correspondence to Dr Rory Collins, Clinical Trial Service Unit, Radcliffe Infirmary, Oxford OX2 6HE.

Accepted for publication 26 March 1991

Abstract

Consultant physicians and cardiologists were surveyed early in 1987 and 1989 to document the management policies for the treatment of acute myocardial infarction in United Kingdom hospitals and to assess the influence of major clinical trials on these policies. The response rate to both these surveys was high (84% (1178 physicians) in 1987 and 76% (982 physicians) in 1989). The percentage of physicians that reported using antiplatelet therapy "routinely" in acute myocardial infarction rose from 9% in 1987 to 84% in 1989 while those who reported using it "rarely or never" fell from 42% to 3%. Similarly, "routine" use of fibrinolytic therapy rose from 2% to 68%, and use "rarely or never" fell from 53% to 3%. This increase in the reported use of fibrinolytic therapy was accompanied by greater certainty about its efficacy and relative safety and by a general widening of the indications for its use. The use of other treatments in acute myocardial infarction (for example, the general use of anticoagulants, β blockers, nitrates, calcium antagonists, or prophylactic antiarrhythmic agents) seemed to change little during this period, although the routine use of coronary angiography and oral anticoagulants after fibrinolytic therapy fell substantially between 1987 and 1989 (from 23% to 4%, and from 24% to 7% respectively).

Fibrinolytic and antiplatelet therapy were accepted into the routine management of myocardial infarction during a relatively short period that coincided with the reporting of several positive controlled trial results. Clinical trials have rarely been seen to have had such a great impact on practice. In this case the rapid acceptance of the trial results may have been due to the consistency and reliability of the estimates of the size of the benefits (and risks) of therapy seen in these unusually large studies.

More than 100 000 patients are admitted to United Kingdom hospitals each year with a diagnosis of suspected acute myocardial infarction.[1] Of these, a few tens of thousands will die during the hospital admission or in the subsequent months. Consequently, a substantial research effort is being made to identify treatments for acute myocardial infarction (such as β blockers,[2] fibrinolytic therapy,[3–6] antiplatelet therapy,[4] vasodilator therapy,[7] anticoagulants,[8] calcium antagonists,[9] antiarrhythmics,[10] and angioplasty[11–13]) that might reduce morbidity and mortality. There is, however, little direct evidence[14–16] about current cardiological practice in the United Kingdom, or of any changes that might be occurring as the results from major clinical trials emerge. To investigate these points we conducted two surveys among United Kingdom consultant physicians and cardiologists of their treatment policies for acute myocardial infarction, first in early 1987 and then again in early 1989.

Methods

1987 SURVEY

The index of hospitals section of *The Medical Directory 1985* was used to help identify all consultant physicians and cardiologists in Britain and Northern Ireland who might be involved in the care of patients with acute myocardial infarction. In mid-1986 a regionally representative random sample of 50 of these physicians was sent a pilot questionnaire to gauge the likely response and to modify any questions that caused confusion or other difficulties. A modified five page questionnaire was then sent in December 1986 to all the consultants identified and a reminder was sent in March 1987 to those who had not replied. Of 1984 consultants written to initially, 1248 replied to the first letter and a further 417 replied to the reminder (84% overall response rate). Four hundred and eighty four stated that they did not routinely treat acute myocardial infarction and three had retired (25% of those replying to the first letter and 41% of those replying to the reminder, which suggests that many of the remaining non-responders do not routinely treat acute myocardial infarction: indeed, in the 1989 survey 145 of the 319 non-responders did reply and 40% did not treat acute myocardial infarction). This leaves 1178 who provided details of their current approach to the treatment of acute myocardial infarction in early 1987.

1989 SURVEY

The same questionnaire was sent again in 1989 to the 1178 consultants who stated in response to the first survey that they treated acute myocardial infarction and to the 319 who had not replied to the first questionnaire. Of these 1497 consultants, 787 replied to the first letter and a further 346 replied to the reminder (76% overall response rate). One hundred and fifty one stated that they did not routinely treat acute myocardial infarction (or were retired), leaving 982 that did.

Results

DESCRIPTION OF THE RESPONDENTS

In both surveys combined, 11% of the respondents described themselves as cardiologists and a further 17% as general physicians with a special interest in cardiology. Hence the vast majority (72%) of consultant physicians treating acute myocardial infarction in the United Kingdom do not have a special interest in cardiology. Almost all (99%) of the respondents were either fellows or members of the Royal College of Physicians and 46% had doctorates. Thirty five per cent worked in specialist cardiac centres or university teaching hospitals. Most (88%) admitted patients to some form of coronary care unit, but only about one third had access to facilities for cardiac catheterisation (36%) or coronary angioplasty (26%) and there was little reported change in these facilities between the surveys.

Randomised clinical trials of the treatment of acute myocardial infarction are being conducted in many hospitals in the United Kingdom and more than one third of the consultants reported being involved in at least one such study (most being multicentre collaborations).

TREATMENT USED FOR ACUTE MYOCARDIAL INFARCTION

The physicians surveyed were asked whether, provided there was no specific medical contraindication, they used any of a variety of treatments "routinely for most patients", "sometimes (or as part of a randomised trial)", or "rarely or never" in patients with suspected acute myocardial infarction. Table 1 shows the distribution of responses to these questions.

For **anticoagulants, β blockers, nitrates, calcium antagonists, and prophylactic antiarrhythmics** there was little difference between the results of the 1987 and the 1989 surveys, and the results of the two surveys are considered together. **Anticoagulation:** similar proportions of physicians reported that they used subcutaneous heparin "routinely", "sometimes", and "rarely". In contrast, intravenous heparin and oral anticoagulants were used routinely by ⩽10%. **β Blockers:** these were started routinely in hospital by about a quarter of the consultants and most of the rest used them sometimes. β Blockade was, however, rarely started with an initial intravenous dose. **Nitrates:** oral nitrates were used routinely by about one quarter of the physicians, but intravenous nitrates were used routinely by only about 10%. Most of the other physicians reported that they used nitrates only when there were further clinical indications other than merely suspected acute myocardial infarction. **Calcium antagonists and prophylactic antiarrhythmics:** these were not often used routinely in acute myocardial infarction (6% and 2% respectively in 1987, and 7% and 1% respectively in 1989), and more than half of the consultants responded that they rarely or never used them.

For **antiplatelet** and **fibrinolytic** treatment, in contrast, there seems to have been a

Table 1 Physicians' responses to questions relating to current practice (1178 in 1987 and 982 in 1989)
"In the treatment of ACUTE MYOCARDIAL INFARCTION, do you generally use any of the following agents, provided there are no specific medical contraindications?"

	Percentage of physicians who replied that they used treatment					
	Routinely for most patients		*Sometimes (or as part of a randomised trial)*		*Rarely or never*	
Treatments	*1987*	*1989*	*1987*	*1989*	*1987*	*1989*
Antiplatelet	9	84	49	13	42	3
Fibrinolytic therapy.						
Intravenous	2	68	45	28	53	3
Intracoronary	0	1	6	3	94	96
Anticoagulants						
Subcutaneous heparin	41	38	34	40	25	22
Intravenous heparin	6	11	55	58	38	32
Oral	4	3	40	43	56	54
β Blockers						
Oral	25	31	63	58	11	11
Intravenous	4	3	38	30	58	67
Nitrates						
Cutaneous	3	2	38	32	59	66
Oral	23	27	66	64	11	9
Intravenous	5	12	75	80	20	8
Calcium antagonists:						
Oral	6	7	77	73	18	20
Intravenous	1	1	28	21	71	78
Prophylactic antiarrhythmics	2	1	48	44	50	55

Table 2 Factors that might influence use of intravenous fibrinolytic therapy among those physicians who used it "routinely" or "sometimes" (530 in 1987 and 933 in 1989)

	*Percentage of physicians replying**					
	Yes		*Not sure*		*No*	
Patient characteristics	*1987*	*1989*	*1987*	*1989*	*1987*	*1989*
Site of infarct	11	6	13	6	76	89
Age of patient	69	54	12	9	20	37
Delay from symptoms	93	99	3	1	4	1

substantial change in the physicians' policies between 1987 and 1989. Routine use of antiplatelet therapy increased from only 9% of physicians in 1987 to 84% in 1989—and almost all who did not use it "routinely" in 1989 reported that they did use it "sometimes" for particular patients. A similarly striking increase in fibrinolytic treatment has been seen, with "routine" use increasing from 2% in 1987 to 68% in 1989, with most of those who did not use fibrinolytic therapy "routinely" in 1989 using it "sometimes" for particular patients. Hence, by 1989 almost all of those physicians reported that, for all or some of their patients, they would use antiplatelet and fibrinolytic therapy (97% and 96% respectively).

Given the considerable research interest in fibrinolytic treatment over the past few years, factors that might influence its use were investigated in greater detail in both surveys. Those consultants who said they used it routinely or sometimes were asked if their decision to do so was influenced by the site of infarction, by the patient's age, or by the delay from onset of symptoms to presentation (table 2). Few of the respondents were definitely influenced by the site of infarction, and the proportions that were so influenced decreased from 11% in 1987 to 6% in 1989. The age of the patient influenced about two-thirds of the consultants who answered this question in 1987 but influenced only half of those who responded in 1989. Of those influenced by age in 1987, only 18% treated patients aged over 70 and only 2% treated those aged over 75 (fig 1). Treatment of elderly patients had been adopted more widely by 1989 with 42% treating those aged over 70 and 8% those aged over 75. Delay from the onset of symptoms to presentation seems to play an important part in determining whether fibrinolytic therapy is used: 93% and 99% of respondents in 1987 and 1989 respectively said that it influenced their decision. Patients presenting after six hours were, however, much more likely to be treated in 1989 than they were in 1987 (46% in 1989 compared with only 18% in 1987), and by 1989 about a fifth were using fibrinolytic therapy in patients presenting up to 24 hours after pain onset (fig 2).

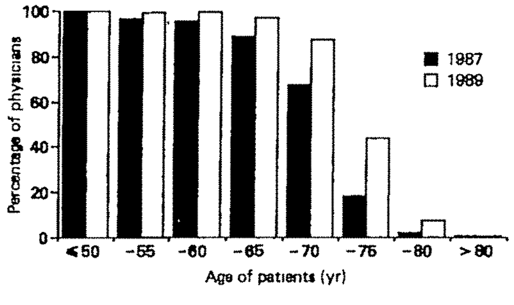


Figure 1 Influence of age of patient on use of fibrinolytic therapy. Percentage of physicians for whom age is a factor (285 of 415 replying to this question in 1987 and 486 of 907 in 1989) who used fibrinolytic therapy in patients of different ages

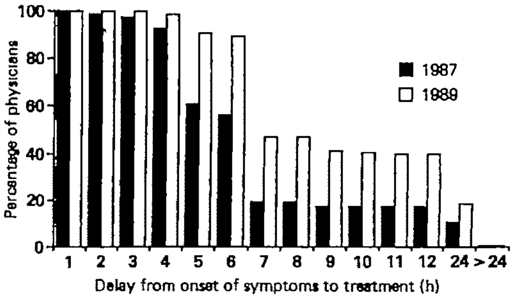


Figure 2 Influence of delay from onset of symptoms on use of fibrinolytic therapy. Percentage of physicians for whom delay is a factor (405 of 436 replying to this question in 1987 and 909 of 924 in 1989) who used fibrinolytic therapy after different lengths of delay.

About a third of the responders used heparin routinely after fibrinolytic therapy, about a third used it sometimes, and about a third rarely or never used it, and there was little change between 1987 and 1989 (table 3). In 1987, 24% of physicians stated that they routinely used oral anticoagulants after fibrinolysis, but this had fallen to only 7% by 1989. As with the acute use of antiplatelet therapy, there was a big increase between 1987 and 1989 in the reported use of antiplatelet therapy after fibrinolysis, with 88% using it routinely in 1989. Interestingly, both coronary angiography and coronary angioplasty after fibrinolysis were reported to be less commonly used in 1989.

Table 4 shows the responses to enquiries about the reasons why some physicians use fibrinolytic therapy "rarely or never". In 1987 about a half of the 594 consultants who rarely or never used fibrinolytic therapy stated that they were unsure about either the beneficial or the adverse effects of treatment. A quarter considered there to be no clear evidence of an early mortality benefit, and more than a half remained unconvinced about any long-term benefit. Very few considered there to be an increased risk of reinfarction, stroke, hypotension, or arrhythmia (9%, 11%, 11%, and 6% respectively), but more than a third thought that fibrinolytic therapy increased the risk of non-cerebral bleeds and of allergies. Nearly a third believed that the currently available intravenous fibrinolytic therapy regimens were not practical in their hospital. By 1989, far fewer physicians (n = 31) "rarely or never" used fibrinolytic therapy, and even among those there was a consensus that fibrinolysis can save lives. For this small number of physicians, the main concerns seemed to relate to the risk of non-cerebral bleeds, as well as to the impracticability of fibrinolytic treatment in their hospitals.

Responses to the questionnaire were considered among various categories grouped according to various features of the physicians (including age, qualifications, degree of specialisation, type of hospital), but this did not identify any group that was much more likely or much less likely to use any of the treatments listed in table 1 (data not shown).

Table 3 Treatment used after fibrinolytic therapy among those physicians that used it "routinely" or "sometimes" (530 in 1987 and 933 in 1989)

	Percentage of physicians replying					
	Routinely		*Sometimes*		*Rarely or never*	
Treatments	*1987*	*1989*	*1987*	*1989*	*1987*	*1989*
Subcutaneous heparin	23	30	22	25	55	45
Intravenous heparin	40	31	32	27	28	42
Oral anticoagulants	24	7	33	26	44	67
Antiplatelet therapy	18	88	59	8	23	5
Coronary angiography	23	4	48	62	29	33
Coronary angioplasty	4	0	58	54	37	46

Discussion

SUMMARY OF RESULTS

The high response to these surveys of United Kingdom consultant physicians and cardiologists routinely treating acute myocardial infarction makes it likely that the results are at least reasonably representative of the opinions of those responsible for the treatment of acute myocardial infarction in hospital. Of course, such surveys provide information only about what people say they do and not necessarily about what they actually do, but in some cases it is possible to determine how reasonable the responses are. For example, where available, the total sales of particular drugs or less representatively the reported use of treatments among patients being studied in experimental protocols can be compared with the survey responses. For fibrinolytic therapy, sales data do reinforce the results of the surveys.[17] Between 1984 and 1987 streptokinase sales were unchanging and sufficient to treat only a few thousand patients with acute myocardial infarction each year, even if it is assumed that none of this streptokinase was used for other indications. But during 1988 there was a substantial increase in sales such that in 1989 the equivalent of more than 50 000 patient treatments were sold in England and Wales. Information from multicentre clinical trials[2,4,18] conducted during this period in Britain also supports the survey responses, in particular confirming the very low routine use of intravenous β blockers, of intravenous nitrates, and (at least before 1989) of antiplatelet agents.

The results of the first survey contrast strongly with a similar survey carried out in spring 1987 among United States physicians,[19,20] in which 66% of 1065 respondents said that they used fibrinolytic therapy routinely at that time. The percentages of United States cardiologists who said that they routinely used prophylactic antiarrhythmics (29% in the United States survey versus 2% in our 1987 United Kingdom survey), intravenous β blockers (16% *v* 4%), oral β blockers (77% *v* 25%), and antiplatelet therapy (63% aspirin and 21% dipyridamole *v* 9% for any antiplatelet) in hospital were also substantially higher than among their United Kingdom counterparts. This may reflect different attitudes to therapeutic intervention in acute myocardial infarction in the two countries—with United Kingdom doctors generally being more sceptical. But another possible explanation is that because four fifths of the United States physicians surveyed did not reply the results of the United States questionnaire may be somewhat unrepresentative. The United States survey also found that although most of the physicians who responded did report that they were using fibrinolytic therapy routinely, they were doing so in only a very small proportion of the patients that presented to them with suspected acute myocardial infarction. This finding is reinforced by 1989/1990 sales data for the United States which indicate that the number of fibrinolytic doses sold in the United States was only about twice as many as in the United Kingdom,[17] despite about a fivefold greater number of myocardial infarction hospital admissions.[1]

IMPACT OF TRIAL RESULTS ON CLINICAL PRACTICE

Discrepancies between the results of clinical trials and the application of those results to clinical practice are not uncommon. It is not known which factors determine the translation of clinical trial results into routine medical practice, but two factors that may be important are the perceived reliability of the study results and the balance between the size of any benefits and the size of any risks.

Many previous trials have failed through inadequate sample size to provide convincing evidence as to whether the treatment under investigation produced a medically worthwhile effect or not.[21,22] The large GISSI-1 study reported a highly significant reduction in mortality with fibrinolytic therapy in the *Lancet* in

Table 4 Attitudes about intravenous fibrinolytic therapy among those consultants who "rarely or never" used it (594 in 1987 and 31 in 1989)

	Percentage of physicians replying:					
	Agree		*Not sure*		*Disagree*	
Physician attitudes	*1987*	*1989*	*1987*	*1989*	*1987*	*1989*
Intravenous fibrinolytic therapy does not reduce						
—early mortality	28	13	51	39	21	48
—long-term mortality	52	13	43	52	5	35
Intravenous fibrinolytic therapy increases risk of.						
—reinfarction	9	0	50	60	41	40
—stroke	11	10	54	57	35	33
—non-cerebral bleed	42	43	42	29	16	29
—allergy	32	14	47	52	21	33
—hypotension	11	5	58	58	32	37
—arrhythmia	6	0	58	63	36	37
—other adverse event	2	0	72	57	26	43
Treatment is not practicable in my hospital	32	26	22	19	46	56

January 1986,[3] yet by the time of our first survey (that is, about 12 months later) this had not led to widespread use. Perhaps it is that the delay between the publication of promising results and their main effect on clinical practice in the United Kingdom is measured in years rather than in months (particularly if, as was the case with GISSI-1, United Kingdom doctors are not involved in the study). It may be, however, that individual trials on their own are not wholly convincing (indeed, the editorial[23] accompanying the GISSI-1 report stated "it is a good principle never to base clinical practice on a single clinical trial"), and that it was the confirmation of the GISSI-1 results by several other positive fibrinolytic therapy trials[4-6] (involving many United Kingdom hospitals) that convinced British physicians to use fibrinolytic therapy routinely.

The need for independent confirmation may explain why the use of intravenous β blockers in acute myocardial infarction has not been adopted widely into routine United Kingdom clinical practice. For this treatment has only been clearly shown to reduce mortality in the ISIS-1 trial,[2] with no other trial of intravenous β blockers large enough to detect reliably an effect of the size seen. (In contrast, several trials of *oral β* blockers started after the acute event showed a significant mortality benefit,[24] and such treatment is used widely.) It may be, however, that the proportional reduction in mortality seen with intravenous β blockers was considered to be too small (15% in ISIS-1 among relatively low risk patients, with a lower 95% confidence limit for this estimate that did not clearly exclude "no worthwhile benefit," compared with a very reliably demonstrated reduction of about 25% with fibrinolytic therapy among both high and low risk patients) to outweigh the perceived risks. The balance between the perceived benefits and perceived risks of treatment may be an important influence on the uptake of clinical trial results. Indeed, it seems likely to explain why, despite results being available from only one clinical trial in acute myocardial infarction,[4] antiplatelet therapy (which was observed to reduce mortality by about as much as fibrinolytic therapy, but with fewer side effects) has been so widely and so rapidly accepted into routine clinical practice. In contrast, uncertainty about the risk: benefit ratio of fibrinolytic therapy may have been important in delaying its widespread adoption and may have limited treatment to those patients for whom the benefits were considered likely to be greatest. Concerns about the safety of fibrinolytic therapy at the time of the first survey in early 1987 seemed to have abated by early 1989 (perhaps due to generally reassuring results emerging from each of the fibrinolytic trials), with the result that not only did many more doctors report that they were using fibrinolytic therapy routinely but also that it was being used in a larger proportion of patients.

About a quarter of the physicians who reported "rarely or never" using fibrinolytic therapy said that one reason was that it was not practicable in their hospitals. This factor may also have played a part in determining the relative speed of uptake of fibrinolytic and of antiplatelet therapies. Low dose oral aspirin is cheap and easy to give, whereas fibrinolytic therapy is costly (even unpatented streptokinase is about £80, while the patented fibrinolytic agents are about £500 for anistreplase and about £800 for tissue plasminogen activator) and involves an intravenous infusion. Those doctors and hospitals that were reluctant to use fibrinolytic therapy because of cost and other practical issues may, therefore, have started to use it in some of their patients only after the benefits became overwhelmingly clear. Some uncertainty still remains as to the cost effectiveness of fibrinolytic therapy in certain categories of patient (for example, those presenting late after the onset of symptoms, or the elderly) and as a result many such patients are not treated. This may be resolved by further consideration of the current trial results, preferably in systematic overviews,[25] and/or by further clinical trials (such as ISIS-3, EMERAS, and LATE) of fibrinolytic versus control in those categories of patient in which uncertainty remains.

In conclusion, the present survey results document a dramatic change in the treatment of acute myocardial infarction in United Kingdom hospitals between 1987 and 1989. In spite of some scepticism about the influence of clinical trials on clinical practice, it is apparent that their findings can produce rapid and substantial changes in treatment, provided the results are seen to be reliable and to indicate medically worthwhile benefits that outweigh any serious risks or other difficulties.

We thank all those doctors who co-operated with the survey by completing and returning the questionnaire; the British Heart Foundation for their support; the ISIS trial office (Paul Appleby, Heather Halls, Deborah Jackson) in the MRC/ICRF Clinical Trial Service Unit, University of Oxford, for processing the questionnaires, Richard Peto and Peter Sleight for their helpful comments; and Gale Mead for typing the article.

1 *Hospital in-patient enquiry Summary tables* London Department of Health and Social Security, 1984
2 ISIS-1 Collaborative Group. Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction ISIS-1 *Lancet* 1986,ii 57–66.
3 Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction *Lancet* 1986,i·397–402.
4 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. ISIS-2. *Lancet* 1988,ii:349–60
5 AIMS Trial Study Group Effect of intravenous APSAC on mortality after acute myocardial infarction. preliminary report of a placebo-controlled trial. *Lancet* 1988,i 545–9.
6 ASSET Study Group Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. *Lancet* 1988,ii.525–30
7 Yusuf S, Collins R, MacMahon S, Peto R Effect of intravenous nitrates on mortality in acute myocardial infarction an overview of the randomised trials *Lancet* 1988,i 1088–92
8 MacMahon S, Collins R, Knight C, *et al* Reduction in major morbidity and mortality by heparin in acute myocardial infarction [Abstract] *Circulation* 1988,78 II–98.
9 Held PH, Yusuf S, Furberg CD Calcium channel blockers in acute myocardial infarction and unstable angina an overview. *BMJ* 1989;299 1187–92
10 MacMahon S, Collins R, Peto R, *et al.* Effects of prophylactic lidocaine in suspected acute myocardial infarction an overview of results from the randomised controlled trials *JAMA* 1988;260 1910–6
11 Simoons ML, Arnold AER, Betriu A, *et al* Thrombolysis with tissue plasminogen activator in acute myocardial infarction no additional benefit from immediate percutaneous coronary angioplasty. *Lancet* 1988;i:197–203
12 TIMI Study Group. Comparison of invasive and con-

servative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II trial. *N Engl J Med* 1989;**320**:618–27.

13 Topol EJ, Califf RM, George BS, *et al* A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 1987,**317**.581–8.

14 Baber NS, Julian DG, Lewis JA, Rose G. Beta-blockers after myocardial infarction have trials changed practice? *BMJ* 1984;**289**:1431–2.

15 Hutchison SJ, Cobbe SM. Management of myocardial infarction in Scotland. have clinical trials changed practice? *BMJ* 1987;**294**:1261.

16 Burrell CJ, Skehan JD, Cowley ML, Barrett CW, Mills PG. Districts' use of thrombolytic agents *BMJ* 1990;**300**: 237–8

17 *Streptokinase quarterly sales in England and Wales*. Source. IMS Audit Data (Hospital sales).

18 Wilhelmsen L, Collins R, Peto R, Sleight P for the ISIS Trials Collaborative Group Drug treatment in hospital and at discharge in the ISIS-1 and ISIS-2 trials [abstract]. *Eur Heart J* 1989;**10**(abstract suppl).116.

19 Hlatky MA, Cotugno HE, Mark DB, *et al*. Trends in physician management of uncomplicated acute myocardial infarction, 1970 to 1987 *Am J Cardiol* 1988,**61**.515–8

20 Hlatky MA, Cotugno H, O'Connor C, *et al*. Adoption of thrombolytic therapy in the management of acute myocardial infarction *Am J Cardiol* 1988,**61**.510–4.

21 Yusuf S, Collins R, Peto R, *et al* Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials *Eur Heart J* 1985,**6**:556–85.

22 Yusuf S, Collins R, Peto R Why do we need some large, simple randomized trials? *Stat Med* 1984,**3** 409–20

23 Streptokinase in acute myocardial infarction. *Lancet* 1986;**i** 421–2.

24 Yusuf S, Peto R, Lewis R, Collins R, Sleight P Beta blockade during and after myocardial infarction an overview of the randomized trials *Prog Cardiovasc Dis* 1985;**27** 335–71

25 Collins R, Gray R, Godwin J, Peto R. Avoidance of large biases and large random errors in the assessment of moderate treatment effects: the need for systematic overviews. *Stat Med* 1987;**6** 245–50

Br Heart J 1991,66·256–60

LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words*
- *In general, no letter should contain more than six references (also typed with double spacing)*

Left ventricular filling dynamics during dipyridamole induced myocardial ischaemia

SIR,—Shahi *et al* (*British Heart Journal* 1991;65:265–70) found altered pulsed Doppler transmitral flow profiles during myocardial ischaemia provoked by dipyridamole stress compared with controls and patients with coronary disease in whom ischaemia was not so induced The interpretative difficulties and limitations of this approach in relation to the method used merit further comment.

Patient age, which importantly influences the filling pattern,[1] was lower in controls than in patients with coronary disease (45 (12) *v* 58 (6) years, p = 0 002). The consequences of dipyridamole induced haemodynamic changes on transmitral flow are therefore also likely to be affected by age. Age data are not given for the various groups and subgroups of the study population Nor are we told whether all the subjects were in sinus rhythm.

Numerous factors can confound the evaluation of filling dynamics after dipyridamole infusion including the administration of aminophylline, which has positive inotropic and vasodilator properties, and fusion of early and atrial waves with tachycardia. How many patients received aminophylline and at what time in relation to the collection of Doppler data and how many developed a single filling wave? In addition, new transient mitral regurgitation is a well recognised consequence of dipyridamole induced ischaemia[2] and profoundly affects the filling pattern but was not sought by these investigators.

Chest pain and electrocardiographic changes were used as markers of ischaemia but are generally believed to be insensitive for this purpose.[3] Transient regional asynergy on cross sectional echocardiography is best but no data on wall motion are given. Furthermore, Shahi *et al* attribute the altered filling response seen in group 3B to more pronounced ischaemia without any supporting evidence. A more likely explanation is the substantially different pre-infusion filling pattern in this subgroup.

The determination of baseline (temporal) variability is fundamental in studies of serial measures. Shahi *et al* have overlooked this and quote only intraobserver variability which takes no account of variation in Doppler indices owing to physiological and technical factors.

We studied 34 patients in sinus rhythm during dipyridamole stress and compared age matched coronary disease patients who developed ischaemia, detected by echocardiographic and electrocardiographic criteria, with those who did not.[4] Transmitral flow was uninterpretable in three (9%) patients owing to fusion of the early and atrial waves. Doppler filling variables were insensitive in identifying patients with ischaemia induction even when this was severe. Our data strongly suggested that changes in ventricular loading and heart rate induced by dipyridamole masked the expected effects of myocardial ischaemia on the filling profile. Other workers have reached similar negative conclusions[5] indicating that this approach cannot supplement wall motion analysis for the evaluation of patients with coronary artery disease Despite reservations on interpretability, the data from Shahi *et al* are consistent with these observations and highlight the ease with which spurious differences between groups may emerge when numerous confounding variables are operative and group size is small.

PETER MAZEIKA
CELIA M OAKLEY
Clinical Cardiology Unit,
Hammersmith Hospital and Royal Postgraduate
Medical School,
DuCane Road,
London W12 0NN

1 Bryg RJ, Williams GA, Labovitz AJ. Effect of aging on left ventricular diastolic filling in normal subjects *Am J Cardiol* 1987;59:971–4
2 Tomimoto S, Takeuchi M, Fukuzaki H. Non-invasive assessment of left ventricular diastolic filling in coronary artery disease by Doppler dipyridamole-stress testing *Jpn Heart J* 1989,30.765–78
3 Picano E Dipyridamole-echocardiography test historical background and physiologic basis *Eur Heart J* 1989,10 365–76
4 Mazeika P, Nihoyannopoulos P, Joshi J, Oakley CM Evaluation of dipyridamole-Doppler echocardiography for detection of myocardial ischaemia and coronary artery disease *Am J Cardiol* (in press)
5 Grayburn PA, Popma JJ, Pryor SL, Walker BS, Simon TR, Smitherman TC Comparison of dipyridamole-Doppler echocardiography to thallium-201 imaging and quantitative coronary arteriography in the assessment of coronary artery disease *Am J Cardiol* 1989;63·1315–20

This letter was shown to the authors, who reply as follows·

SIR,—Dr Mazeika and Dr Oakley quite rightly have brought attention to the differences in age between the control and study group which may have had an affect on our results. Both age and heart rate are well known to be major determinants of transmitral Doppler filling velocities and as yet no correction factors are known to allow for these variables. Neither is it known how heart rate affects subjects of different ages or how heart rate affects patients with abnormal filling velocities in different age groups Despite these unknown variables we feel that useful information can be derived from studying filling velocities during myocardial ischaemia

All patients studied were in sinus rhythm and remained in sinus rhythm during the study period.

Aminophylline was given to two patients in group 3A and one patient in group 3B. In two of these patients it was given at the end of the study period and therefore would not have affected the filling velocities

Two patients in the control group developed a single filling velocity during the study period but only for a maximum of two readings. In these patients the filling velocity of the early filling wave just before merging of the waves was taken to represent the filling velocity.

To allow for baseline temporal variability the mean value of five one minute recordings was taken to represent baseline value

Regional wall motion abnormalities were not specifically assessed in our study but their importance as a more sensitive marker of ischaemia was discussed in the discussion section (p 270)

Reference 5 quoted by Dr Mazeika and Dr Oakley was cited in our paper together with its limitations. We cannot comment on reference 4 at present

Although it was not possible for technical reasons to assess the presence of mitral regurgitation during myocardial ischaemia in our study, Dr Mazeika and Dr Oakley are correct to state that this may have affected our results. Ischaemia-induced mitral regurgitation would increase left atrial pressure and therefore decrease the isovolumic relaxation period and subsequently increase the transmitral pressure gradient with a resulting increase in the early filling velocity and a possible decrease in the atrial filling velocity. It is therefore possible that this may be the reason for the difference in left ventricular filling velocities in groups 3A and 3B Both at the end of the abstract and in the discussion section we stated that our observations could be attributable either to the degree of myocardial ischaemia or to different haemodynamic changes occurring during myocardial ischaemias

Once again we would like to emphasise that the study was designed to observe the left ventricular filling characteristics during myocardial ischaemia and not to suggest that these changes in filling velocities could predict myocardial ischaemia in an individual patient (last paragraph p 269).

I hope these comments will help clarify the points made by Dr Mazeika and Dr Oakley

M SHAHI
Department of Cardiology,
St Mary's Hospital,
Praed Street,
London W2 1NY

Circadian variation in the frequency of onset of chest pain in acute myocardial infarction

SIR,—Dr Thompson and colleagues make a convincing case in Leicester for a midnight peak in onset of myocardial infarction in addition to the well-known one at 8 am (*British Heart Journal* 1991;65:177–8). They try to persuade us that meta-analysis of other studies would confirm this Unfortunately they have omitted from their references perhaps the largest study of all[1] This was the collected data from the World Health Organisation Regional Office for Europe Heart Attack Registers of the 1970s covering some 10 000 events The pooled data from these show a clear peak between 8 and 10 am on weekdays which is much sharper at 10 am on Saturdays and Sundays. There is also a bulge around 4–5 pm but no overall peak around midnight The exception interestingly is a possible such peak on Saturday

If the Leicester peak is not just a chance finding, and it is found in some cities but not others and may be related to Saturdays, one wonders whether it is related to closing time in public bars.

HUGH TUNSTALL-PEDOE
Cardiovascular Epidemiology Unit,
Ninewells Hospital and Medical School,
Dundee DD1 9SY

1 World Health Organisation Regional Office for Europe. Myocardial Infarction Community Registers Public Health in Europe 5 Copenhagen, 1979.

This letter was shown to the authors, who reply as follows:

Sir,—We thank Professor Tunstall-Pedoe for his interesting comments on our paper The confirmation of the finding of a secondary midnight peak in the onset of chest pain in acute myocardial infarction in a five year retrospective anaalysis of a five year prospective study makes it unlikely that the peak is a chance finding Our discussion reaches no conclusion about its possible cause but our data do not exclude the possibility that the midnight peak is a local phenomenon whose explanation might lie in local circumstances. We find the explanation in terms of public house closing times intriguing but unlikely to be correct. Our data, which have also been analysed for the frequency of acute myocardial infarction on days of the week (unpublished), do not provide significant support for the Saturday hypothesis. Moreover, a change of licensing hours applied to Leicester which liberalised weekday public house opening, occurred during the prospective data collection and did not result in a measurably stronger trend in support of the midnight peak during the later stages of the study

DAVID R THOMPSON
JURGEN E F POHL
Coronary Care Unit,
Leicester General Hospital,
Leicester LE5 4PW

Syndrome X and hyperventilation

Sir,—Syndrome X and hyperventilation have long been associated, and Lewis and colleagues (*British Heart Journal* 1991; 165:94–6) are to be congratulated for their discriminating contribution to the field and for raising several important questions. A central issue is whether hyperventilation can be dismissed on the basis of a rather limited schedule of testing For example, it is no longer thought that the forced hyperventilation provocation test (FHPT) is the "gold standard" of hyperventilation testing,[1 2] but that provocation by personally relevant stressors[3 4] is at least as important Indeed, in the context of cardiological patients, the latter stressors, which can also activate the adrenergic vasoconstrictive pathways[5] are probably the triggers most relevant in everyday life. Furthermore, besides the interplay between hyperventilation and sympathetic nervous system activation (with consequences such as magnesium depletion[6]) it seems likely that it is the neuroendocrine setting that can determine whether or not a given episode of hyperventilation has vasoconstrictive consequences.[7]

It is a commonplace finding that many patients with recurrent hyperventilation illnesses do not hyperventilate during an exercise test, but readily overbreathe in response to an emotional challenge, particularly when the challenge involves the recall of feelings of being trapped or of anger.[4 7]

As far as the data presented by Lewis *et al* are concerned, besides noting the absence of figures for end tidal pressure of carbon dioxide (Co_2 ET) for their controls, we also note that the Co_2 ET values of 38 mm Hg at 50% of maximum exercise and 37 mm Hg at maximum exercise are well below expected normal values.[8]

The demonstration of increased minute ventilation for given minute carbon dioxide (VE/Vco_2) is quite consistent with chronic hyperventilation. It is due either to reduced respiratory centre buffering[9] or a flywheel effect when regularly over-activated pathways promote breathing,[10] or both. The observation of a raised VE/VCo_2 may well be the key indicator of a longer term tendency to hyperventilation, because as stated above, the FHPT is a single act of hyperventilation and is dependent upon the patient's starting point in terms of other influences upon vasoconstriction such as emotional arousal and depletion of the body's buffering systems.

A basic question about syndrome X patients is whether their responsiveness to recognised vasoconstrictive influences is greater than average, just as Europeans in general are more responsive than the Japanese [11]

We suggest that Lewis *et al* have sharpened the definition of characters in the drama of syndrome X and hyperventilation but have not yet brought down the final curtain

STUART D ROSEN
J C KING
P G F NIXON
Cardiac Department,
Charing Cross Hospital,
Fulham Palace Road,
London W6 8RF

1 King JC, Rosen SD, Nixon PGF Failure of awareness of hypocapnia. *J R Soc Med* 1990,83 765–7
2 Roll M, Zetterquist S Acute chest pain without obvious organic cause before the age of 40 years *J Intern Med* 1990,228 223–8
3 Lewis BI Chronic hyperventilation syndrome *JAMA* 1954,155 1204–8
4 Nixon PGF, Freeman LJ The "think test". a further technique to elicit hyperventilation *J R Soc Med* 1988;81 277–9.
5 Groen JJ The measurement of emotion and arousal in the clinical physiological laboratory and in clinical practice In Levi L, ed. *Emotions. their parameters and measurement* New York· Raven Press, 1975·727–46.
6 Ebel H, Gunther T The role of magnesium in cardiac disease *J Clin Chem Biochem* 1983,21 249–56
7 Nixon PGF. Exhaustion cardiac rehabilitation's starting point In Maes S, Spielberger CD, Defares PB, Sarason IG, eds *Topics in health psychology* London John Wiley and Sons, 1986
8 Chambers JB, Kiff PJ, Gardner WN, Jackson G, Bass C Value of measuring end tidal partial pressure of carbon dioxide as an adjunct to treadmill exercise testing *BMJ* 1988, 296 1281–5
9 Brown EB, Jr. Physiological effects of hyperventilation *Physiol Rev* 1953,33 445–71.
10 Folgering H, Colla P Some anomalies in the control of $\text{P}_\text{A}\text{Co}_2$ in patients with a hyperventilation syndrome *Bull Eur Physiopathol Respir* 1978;14:503–12.
11 Maseri A, Kaski JC Pathogenetic mechanisms of coronary artery spasm *J Am Coll Cardiol* 1989,14 610–2

This letter was shown to the authors, who reply as follows:

Sir,—We appreciate the interest shown by Dr Nixon and colleagues in our paper. Our study refers of course to our carefully characterised patients—an important consideration given the widely differing patient groups represented in published reports on patients with unexplained chest pain Clearly the filing category of syndrome X is coming to the end of its useful life, particularly in view of the confusion now arising over a different "syndrome X" [1]

In specific comment on the points raised by Dr Nixon and colleagues—our patients with syndrome X all described typical angina and, in every case, exercise induced the same symptom. We would argue that an exercise test in such a group represents a "personally relevant stressor". The finding of normal arterial Pco_2 values throughout exercise in our syndrome X patients formed the basis for our conclusion that they were not then hyperventilating inappropriately (which in common usage is the implication inherent in the term) Because we showed that end tidal Pco_2 correlated only poorly with arterial Pco_2 in these patients, their end tidal measurements, we agree, provided no evidence either for or against a diagnosis of hyperventilation. Chronic hyperventilation may indeed increase the VE/Vco_2 slope but only in the presence of low arterial Pco_2 (the modified alveolar gas equation states $\text{VE} = 863\ \text{Vco}_2/\text{Paco}_2(1 - \text{V}_\text{D}/\text{V}_\text{T})$. The normal arterial Pco_2 in our patients implies an increase in deadspace ventilation [2] We did not measure arterial Pco_2 in our control patients for ethical reasons.

We share the view that the final curtain is not yet drawn on the various players on this ill-lit stage, while our spotlights continue to weave [3]

N P LEWIS
S J HUTCHISON
N WILLIS
A H HENDERSON
Department of Cardiology,
University of Wales College of Medicine,
Heath Park,
Cardiff CF4 4XN

1 Dean JD, Jones CJH, Hutchison SJ, Peters JR, Henderson AH Syndrome(s) X *Lancet* 1991;337 916
2 Jones NL *Clinical exercise testing* 3rd ed Philadelphia W B Saunders, 1988 13–74
3 Dean JD, Jones CJH, Hutchinson SJ, Peters JR, Henderson AH Hyperinsulineamia and microvascular angina ("Syndrome X") *Lancet* 1991,337 456–7

Alcohol ablation of atrioventricular conduction

Sir,—Dr Cunningham and Dr Rowland (*British Heart Journal* 1991;65.115) favour the use of "conventional" methods of ablation of atrioventricular conduction rather than the new method of ethanol ablation. "Conventional" methods include, according to them, radiofrequency ablation (with its known low success rate), higher energy shocks (with a known high complication rate), and low energy shocks (only three published reports of this—two abstracts and a small series). Long-term results with ethanol ablation remain excellent.[1] No deaths have been reported after alcohol ablation. Its success rate, even when analysed on the basis of intention to treat, is comparable to "conventional" methods. The results of "conventional" methods were never presented on an intention to treat basis.

It looks to me as if there are no "conventional" or "established" methods for the ablation of atrioventricular conduction. Only long-term results will show which method offers the best results at the lowest risk Meanwhile, investigators and physicians should remain open-minded about different treatments.

It takes a long time to become a "classic" or for a treatment to become established or "conventional". We should not allow our biases to make us discard any possibility of treating our patients better.

PEDRO BRUGADA
Cardiovascular Research and Teaching Institute,
Moorselbaan 164,
B-9300 Aalst,
Belgium

1 Brugada P, de Swart H, Smeets J, Wellens HJJ Transcoronary chemical ablation of atrioventricular conduction *Circulation* 1990,81 757–61

Echocardiographic diagnosis of a ruptured aneurysm of the sinus of Valsalva: operation without catheterisation in seven patients

SIR,—Dr Sahasakul and colleagues (*British Heart Journal* 1990;64:195–8) clearly described the echocardiographic diagnosis of a ruptured aneurysm of the sinus of Valsalva, but they made no suggestion about its aetiology other than to label this a disease of "congenital origin". The ruptured sinus affected the right coronary sinus in six of their seven patients. Figure 1 in their article clearly shows the absence of the subpulmonary infundibulum and fibrous continuity between the aortic root and the pulmonary valve (fig 1B), features characteristic of a doubly committed subarterial ventricular septal defect,[1] with protrusion of the right coronary sinus into the right ventricle (fig 1A).

The usually accepted explanation for a congenital aneurysm of the sinus of Valsalva is thinning of the wall of the aortic sinus just above the leaflet hinge,[2] although this alone does not explain why the left coronary sinus is hardly ever involved. The association of the aneurysm .of the sinus of Valsalva with a ventricular septal defect was described in Japan. Sequential changes in morphology were proposed, leading to rupture of the right coronary sinus into the right ventricle in young adulthood when there was a ventricular septal defect in the outlet portion of the septum.[3] It is notable that there is an increased incidence of ruptured aneurysm of the sinus of Valsalva in Oriental populations, just as there is of doubly committed subarterial ventricular septal defect. Large defects without deformity or offsetting of the aortic valve cause major haemodynamic disturbance in infancy, whereas smaller holes typically present in childhood with aortic regurgitation because of prolapse of the right coronary aortic cusp; but they may present with rupture of a sinus of Valsalva aneurysm in adult life.[4] Indeed, during a 10 year period at one Japanese hospital 32 of 36 patients undergoing surgery for a ruptured aneurysm of the sinus of Valsalva had "subarterial infundibular" ventricular septal defects.[5]

Thus it should be emphasised that the likely substrate for aneurysm of the sinus of Valsalva in many patients is the presence of a doubly committed subarterial ventricular septal defect with offsetting of the arterial valves Prolapse of the right coronary aortic cusp results in elongation of the sinus and thinning of the sinus wall just above the leaflet hinge. Mechanical stress leads to dilatation of the sinus over many years, and sometimes rupture into the right heart. Patients with doubly committed subarterial ventricular septal defect and offsetting of the arterial valves, which can be observed echocardiographically, are at risk of this later complication.[4]

IAN D SULLIVAN
MARC R DE LEVAL
Hospital for Sick Children,
Great Ormond Street,
London WC1N 3JH

1 Griffin ML, Sullivan ID, Anderson RH, Macartney FJ Doubly committed subarterial ventricular septal defect. new morphological criteria with echocardiographic and angiocardiographic correlation *Br Heart J* 1988; 59:474–9.
2 Kirklin JW, Barratt Boyes BG Congenital aneurysms of the sinus of Valsalva. In. *Cardiac surgery* New York: John Wiley and Sons, 1986 655–78.
3 Sakakibara S, Konno S Congenital aneurysm of the sinus of Valsalva associated with ventricular septal defect *Am Heart J* 1968,75:595–603.
4 de Leval MR, Pozzi M, Starnes V, Sullivan ID, Stark J, Somerville J, *et al*. Surgical management of doubly committed subarterial ventricular septal defect. *Circulation* 1988;78(suppl III) 40–6
5 Momma K, Toyama K, Takao A, Ando M, Nakazawa M, Hirosawa K, Imai Y. Natural history of subarterlal infundibular ventricular septal defect *A Heart J* 1984,108:1312–7

This letter was shown to the authors, who reply as follows

SIR,—Dr Sullivan and Dr de Leval have correctly pointed out the association between a ruptured aneurysm of the sinus of Valsalva and a doubly committed subarterial ventricular septal defect in most cases reported in the Orient. Nevertheless, there are several other causes of a ruptured aneurysm of the sinus of Valsalva, chiefly a congenital lack of fusion between the media of the aorta and the annulus of the aortic valve.[1] Other reported causes include bacterial endocarditis, Marfan's syndrome, coarctation of the aorta, bicuspid aortic valve, trauma, and also the association with ventricular septal defect.[2-5]

The reason for the high prevalence of ruptured aneurysms of the sinus of Valsalva in Oriental patients is not known. We propose a genetic cause or perhaps a logistic one: patients with ventricular septal defect in the Orient may not see a doctor until symptoms develop—that is after the aneurysm has already ruptured. The latter proposal is particularly true in Thailand because many paediatric patients with ventricular septal defect went unnoticed for several years because they were born in remote provincial areas without modern medical facilities.

YONGYUTH SAHASAKUL
SUPHACHAI CHAITHIRAPHAN
Division of Cardiology,
Siriraj Hospital,
Mahidol University,
Bangkok 10700, Thailand

1 Boutefeu JM, Morat PR, Hahn C, Hanf E. Aneurysms of the sinus of Valsalva. Report of seven cases in review of the literature. *Am J Med* 1978,65:18–24
2 Gonzalez-Lavin L, Scappatura E, Lise M, Ross DN. Mycotic aneurysms of the aortic root. A complication of aortic valve endocarditis. *Ann Thorac Surg* 1970,9:551–61.
3 Steinberg L, Mangiarsi JL, Noble MJ. Aneurysmal dilation of the aortic sinuses in Marfan's syndrome *Circulation* 1967;16:368–73.
4 DeBakey ME, Dietrich EB, Liddecoat JE, Kinard SA, Garret HE Abnormalities of the sinuses of Valsalva experience with 35 cases. *J Thorac Cardiovasc Surg* 1967;54 312–32.
5 Sahasakul Y, Panchavinnin P, Chaithiraphan S, Sakiyalak P Echocardiographic diagnosis of a ruptured aneurysm of the sinus of Valsalva. operation without catheterisation in seven patients. *Br Heart J* 1990;64 195–8.

Impending paradoxical embolism: a rare but important diagnosis

SIR,—I read with interest the recent case report of impending paradoxical embolism by Speechly-Dick *et al.* (*British Heart Journal* 1991;65:163–5). However, I would like to offer two differing opinions on the points they made.

First, their statement that only two of 37 reported cases of paradoxical embolism were diagnosed during life was an underestimation. All of 25 cases reviewed and reported by Leonard *et al*[1] and 10 of 27 cases reviewed by Jungbluth *et al*,[2] cited by the Speechly-Dick *et al* in their paper as references 4 and 6, respectively, were diagnosed during life. The two cases reported by me in 1976 were diagnosed during life.[3]

Second, the current treatment of choice for patent foramen ovale or minute atrial septal defect as a cause of paradoxical embolism is non-surgical transcatheter closure.[4] If this defect could be closed during a cardiac catheterisation, the need for open heart surgery would be obviated together with the extended hospital stay, expense, need for blood, and all the morbidity, mortality, and psychological trauma associated with surgery.

TSUNG O CHENG
Division of Cardiology,
Department of Medicine,
The George Washington University Medical Center,
2150 Pennsylvania Avenue, NW,
Washington, DC 20037, USA

1 Leonard RCF, Neville E, Hall RJC. Paradoxical embolism A review of cases diagnosed during life. *Eur Heart J* 1982;3·362–70.
2 Jungbluth A, Erbel R, Darius H, Rumpelt H, Meyer J. Paradoxical coronary embolism. Case report and review of the literature. *Am Heart J* 1988,116 879–85.
3 Cheng TO. Paradoxical embolism. A diagnostic challenge and its detection during life. *Circulation* 1976,53:565–8.
4 Mullins CE, Benson L, Hellenbrand WE, Perry S, Rocchini AP Therapeutic cardiac catheterization in congenital heart disease. Presented at the American College of Cardiology 40th Annual Scientific Session, Atlanta, Ga on 3 March 1991.

This letter was shown to the author, who replies as follows:

SIR,—Professor Cheng is correct in saying that there are many cases of paradoxical embolism diagnosed in life and reported in the literature. However, our case report described the rare finding of impending embolism of which, to my knowledge, there are only two previously reported cases. The second point which Professor Cheng raised was that in his opinion the current treatment of choice for patent foramen ovale or minute atrial septal defect is non-surgical transcatheter closure. This is a relatively new procedure for which we have, as yet, no long term results. Surgical closure, however, is a well-established and accepted technique with very low mortality and morbidity and excellent long-term results.[1] Non-surgical transcatheter closure may well be the treatment of the future but is not yet the treatment of choice.

M E SPEECHLY-DICK
Department of Cardiology,
Middlesex Hospital,
Mortimer Street,
London W1N 8AA

1 Murphy SG, Gersh BJ, McGoon MD, *et al.* Long-term outcome after surgical repair of isolated atrial septal defect. *N Engl J Med* 1990;323:1645–50.

BOOK REVIEWS

Cardiac Electrophysiology: a Textbook. Prepared in Honor of Brian F Hoffman. Eds Michael R Rosen, Michiel J Janse, and Andrew L Wit. (Pp 1195; $160.00.) Mount Kisco, NY: Futura Publishing Company, 1990. ISBN 0-87993-391-7.

We are all accustomed to seeing books that seem like the present volume but that consist of the proceedings of a meeting. There is a subtle and important difference here; while this books is a festschrift to Brian Hoffman, the contributions were collected beforehand and it has appeared within months of the gathering at which he was honoured. Hoffman had taught and indeed inspired many of the contributors and the central role of his unit at Columbia in diffusing the knowledge of cardiac electrophysiology is well recognised. It must give him considerable satisfaction to see how the basic concepts about which he and Paul Cranefield had written so helpfully more than 30 years ago in their *Electrophysiology of the Heart* have been explored in such considerable detail.

The editors are guilty of two acts of enthusiasm—in this excellent cause—that deserve a brief note. The subtitle "textbook" is not really appropriate for a collection of chapters of diverse origin which tend—helpfully—to overlap; and few students are likely to agree that it can be used as an introductory text to be read "cover-to-cover": for all but those with some knowledge, that would be hard going.

These caveats should be set aside, and the book appraised for what it genuinely is, a superb collection of up to date expert contributions by most of the foremost figures in the field. It is an essential source book for basic scientists and cardiologists who seek well referenced material covering the knowledge that has been acquired over the last century, since Engelmann identified propagation of electrical excitation in cardiac muscle. Naturally, it focuses particularly on the understanding of normal and abnormal impulse generation and conduction made possible by the early microelectrode studies in nerve tissue performed by Hodgkin and Huxley just over 40 years ago. Chapters take you through new and old concepts and define terms that are now found in more general articles in current journals. Here you will find out all about reflection, as opposed to reentry; triggered afterdepolarisations, early and late, and their relevance to clinical events; parasystole; ionic currents, neurohumoral factors; and much more. It is well indexed, the key topics are easy to find, and the explanations are there, though not always as easy to understand as the authors suggest. Perhaps the only redundant material is that on the clinical aspects of the management of arrhythmias, which is not to say that the relevant more basic sections elsewhere are unhelpful.

As one scans other publications that have the same coverage, it is difficult not to find them wanting in comparison with this book. Textbook or not, and introductory text certainly not, this is an unparalleled collection of important contributions that need to be published together. The developments in the field can now be drawn together: they may be hard going for the clinical cardiologist, but looking at the progress achieved since Brian Hoffman and Paul Cranefield took us in the footsteps of the late Gordon Moe in 1960, we will find it helpful and indeed essential to use this book in order to keep aware of what is now accepted as well as of the directions in which knowledge is advancing.

DENNIS M KRIKLER

Lecture Notes on Cardiology. 3rd ed. Aubrey Leatham, Catherine Bull, and Mark V Braimbridge; with a chapter on electrocardiography by Derek J Rowlands and a section on echocardiography by Graham Leech. (Pp x + 342; £12.95.) Oxford: Blackwell Scientific Publications, 1991. ISBN 0-632-01944-1.

The third edition of this compact book, which was first published in 1967, has been extensively rewritten and provided with new illustrations.

By their nature, lecture notes have to be succinct and didactic. This requirement often makes for dull reading. This book continues with its original commitment to the application of physiological principles at the bedside or in the non-invasive cardiac department—each chapter starts with this approach and then moves on to consider the treatment, indications for surgical treatment, the surgery, and the results. This book thereby succeeds in making the reading interesting and educational. It gives sufficient information to allow an understanding of the various conditions discussed. It inevitably will disappoint the reader who is looking for help with a differential diagnosis or help with a management problem

The text is liberally interspersed with excellent line drawing and illustrations of the relevant anatomy or investigations. It is a little disappointing that there are no examples of Doppler studies: the technique is discussed but there are no illustrations.

There are several excellent and comprehensive chapters. In particular, the chapters on electrocardiography, on congenital heart disease, and on disease of the thoracic aorta are very clear with good line drawings.

A major omission from this book is that of prevention of coronary artery disease. The first edition specifically excluded it because it was adequately considered in other books. The present interest in its role, the emerging good evidence of the possibility of reversing the disease process, and the huge advances made in the understanding of lipid metabolism and the role of platelets and the clotting factors should surely earn it a place in a book of this nature. The work "prevention" does not appear in the index.

My only other criticism is that it is perhaps sad that the United Kingdom Resuscitation Council guidelines were not mentioned in the chapter on cardiac emergencies. Some of the recommendations in this book are not entirely consistent with the guidelines.

Despite these criticisms, this book selling at £12 95, is very good value for money and will be very helpful to those looking for a succinct, soundly based, clinical approach to cardiology. It will be of particular use to those studying for their MB or at the membership level as well as to those physicians or general practitioners who need their knowledge refreshed.

D L H PATTERSON

The titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add £2 per item for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (MasterCard, VISA, or American Express) stating card number, expiry date, and your full name.

BRITISH CARDIAC SOCIETY NEWSLETTER

As avid readers of this newsletter will be aware the society recently established a Data Management Committee with John Parker as chairman. It has met on several occasions. Professor Peter Macfarlane has been an active member and has contributed much of the information that follows. One of the aims of the committee was to make suggestions for an agreed minimum cardiological data set that would facilitate audit, clinical control of contracts, and research. To this end, specific tasks have been allocated to members of the committee, who have undertaken to define data sets on cardiac care units, electrocardiography as applied to tracings recorded both at rest and during exercise, invasive cardiology, and cardiac surgery. Because the expertise of the committee cannot cover all areas of cardiology, other members of the society have been approached to help in the work. Assistance has been sought in matters relating to electrophysiology, echocardiography, and nuclear cardiology. Many more areas have yet to be discussed.

As with many new developments, other groups are active in the field even in relation to cardiology. We believe it is important to avoid unnecessary duplication of effort—so coordination with others, including a group under the aegis of the Royal College of Physicians of London, has become a high priority as specific objectives are defined. The committee has also sought liaison with others outside the specialty, and two invited speakers attended the most recent meeting in early July. These were Mr Gerry Gold, a consultant to the National Health Service Information Management Centre in Birmingham with responsibility for Common Basic Specification, and Dr James Read, director of the recently established National Health Service Centre for Coding and Classification.

The Information Management Centre and the National Health Service Centre for Coding and Classification are two of seven divisions of the Information Systems Directorate—the other five have responsibility for strategic planning, projects, implementation, statistics, and hospital information support systems (HISS). Rationalising and, where possible, standardising developments across the National Health Service (that have proceeded in a rushed and piecemeal fashion) is clearly a major task. Most members of the society who are not familiar with the new information systems can be forgiven if they are confused by a plethora of terms that seem designed to hinder comprehension. But this is part of our new world, and it behoves us to attempt to understand it.

Dr Read was until very recently a full time general practitioner. His original ambition was to develop a set of diagnostic codes for use in general practice. But they were perceived to have a much wider application and they received such acclaim that he was encouraged to forsake general practice to become director of the Centre for Coding and Classification, which is based in Leicestershire. The Read code can be mapped on to the older systems such as ICD 9 and OPC 4 but the momentum behind the new method is such that it may well supersede these altogether in due course. It provides a dictionary that can already summarise clinical information in considerable detail: moreover, its structure lends itself to continuing development.

Each Read code has at present up to five characters. The code is hierarchical from left to right with each character offering progressively more detail. The first character defines the broad class, the second character the sub class, and so on. Each of the five characters may be a digit 0 to 9 or a letter a to z or A to Z The letters i and o are excluded to avoid confusion with the digits 0 and 1. This still leaves over 650 million possible codes within the five character framework. An example illustrates the possibilities.

Level	*Term*	*Read*	*ICD-9-CM*
1	Circulatory system disease	G	390–459
2	Ischaemic heart disease	G3	410–414
3	Acute myocardial infarction	G30	410
4	Other acute myocardial infarction	G30y	410 8
5	Acute papillary muscle infarction	G30y1	410 8

Dr Read pointed out that the code was designed primarily to be useful for recording and retrieving clinical information and not specifically for grouping patients according to resource utilisation.

The Read approach allows coding of occupation, history and symptoms, examination and signs, diagnostic and laboratory procedures, and so on—as well as a wide range of diagnoses. In theory, most of the medical record could be coded for ease of storage and retrieval, but the record itself will still be written in English by doctors. The reader will be relieved that we are not expected to face in the ward, catheter laboratory, operating theatre, or outpatient department a sheet composed of a long string of letters and numbers that have replaced ordinary language.

Thirty eight working groups are currently engaged in extending the Read codes. It seems clear that they will become a national standard. The Data Management Committee believe the British Cardiac Society should cooperate with the Centre for Coding and Classification to ensure that the Read classification and descriptive language benefit from the closest cooperation from the specialty. We hope that this objective can be achieved in association with others who have a legitimate interest. At some stage joint working groups may be needed to ratify proposals and to ensure that a wide consensus has been achieved.

We have more news of our plans to provide adequate identification cards for patients with valve replacements. The plan has now been approved by the Executive of the Cardiothoracic Surgeons of Great Britain and Ireland The scheme will operate in cooperation with the valve registry kept by Professor Ken Taylor. A small committee has been set up with representation from cardiology as well as from cardiothoracic surgery, and cooperation is being sought from the valve manufacturers. We envisage that cards, probably similar to credit cards, will be given to every patient. These are likely to show the type and serial number of the valve, to identify the surgical centre, and to give the implantation date, as well as providing the usual demographic data. We hope this can be achieved without cost to the patient or additional expense for the centres.

Plans for the new registrar training programme are moving ahead slowly. Many of the regions have already adopted the lead given by the cardiologists and later by other specialties in making provision for three years' training at registrar level (we look forward to the abolition of the terms "registrar" and "senior registrar", because they are too closely associated with older concepts and thereby obscure the changes that must occur to meet modern needs). Manpower representatives of the major clinical specialties met, under the auspices of the Royal College of Physicians of London, with officers of three regional health authorities and discussed the way forward for the introduction of the new style posts, given the problems and constraints of the cuts in posts for career trainees imposed by the Joint Planning Advisory Committee. We found great goodwill, and we were encouraged to believe that the problems associated with the changes can be overcome fairly quickly. More meetings will be arranged and more news will be forthcoming soon.

Finally, a reminder that the closing *postmark* date for abstracts for the American College of Cardiology (12 April to 16 April 1992, Dallas) is Friday 6 September 1991.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society
1 St Andrew's Place
London NW1 4LB

NOTICES

1992

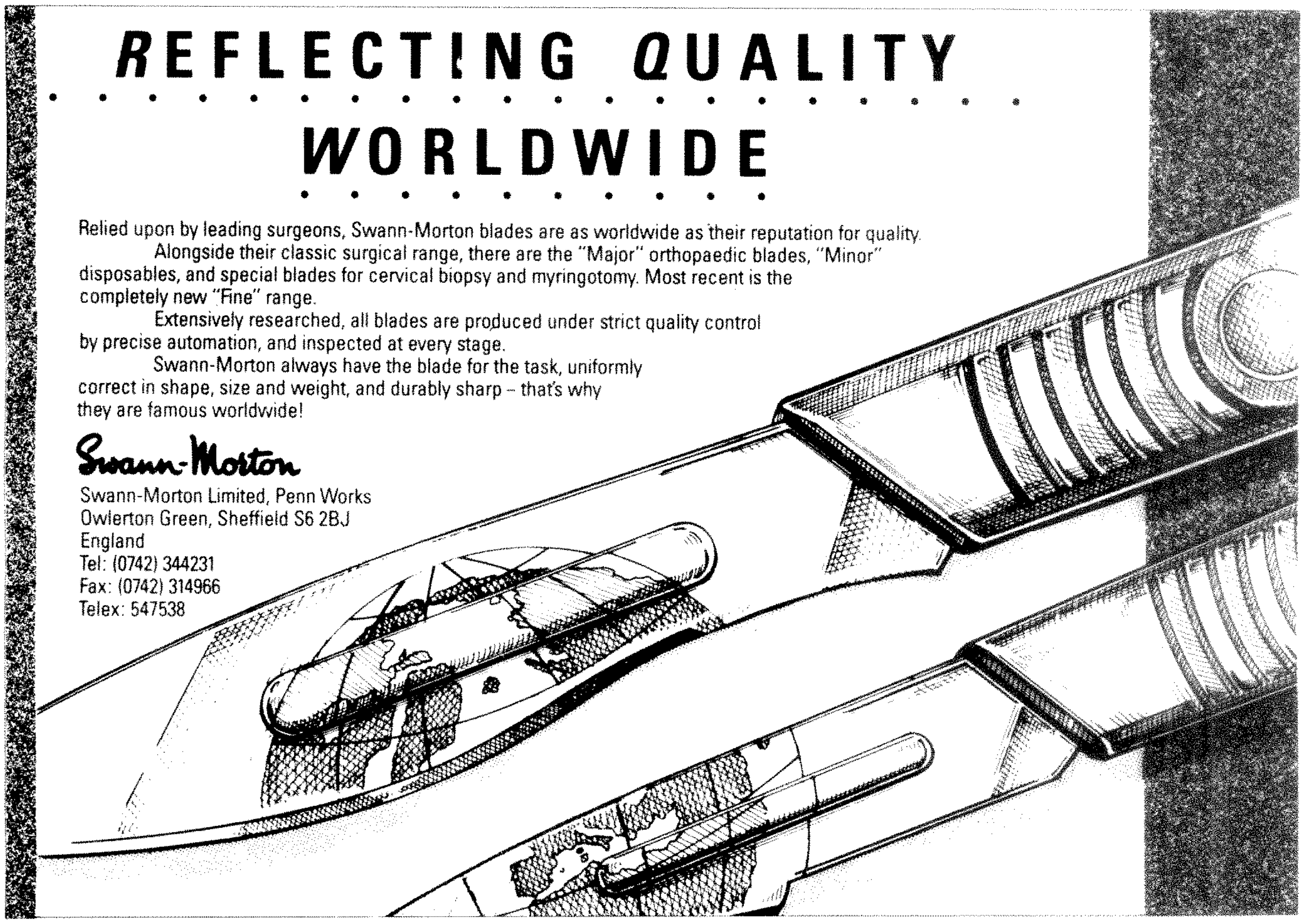
The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre on 26 to 29 May. The closing date for receipt of abstracts is 3 January 1992.

The Arizona Heart Institute will hold its **International Congress V: Strategies in Endovascular Interventions** on 12 to 16 February in Scottsdale, Arizona. The deadline for submission of abstracts is 1 October 1991: Erika Scott, International Congress V, 2632 N 20th Street, Phoenix, AZ 85006 (Tel: 602 266 2200).

The **12th International Symposium on Intensive Care and Emergency Medicine** will be held at the Brussels Congress Centre on 23 to 27 March: Professor J L Vincent, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Bruxelles, Belgium (Tel· 32 2 526 33 80; Fax 32 2 526 45 55).

ACC '92 DALLAS TEXAS · APRIL 12-16

The **41st Annual Scientific Session and Exposition** will be held in Dallas, Texas on 12 to 16 April. The deadline for submission of abstracts is 6 September 1991: American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20814–1699 (Tel: 800 253 4636–301 897 2693).



REFLECTING QUALITY WORLDWIDE

Relied upon by leading surgeons, Swann-Morton blades are as worldwide as their reputation for quality.

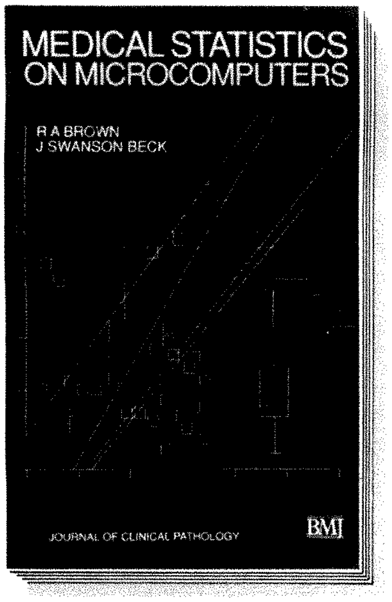
Alongside their classic surgical range, there are the "Major" orthopaedic blades, "Minor" disposables, and special blades for cervical biopsy and myringotomy. Most recent is the completely new "Fine" range.

Extensively researched, all blades are produced under strict quality control by precise automation, and inspected at every stage.

Swann-Morton always have the blade for the task, uniformly correct in shape, size and weight, and durably sharp – that's why they are famous worldwide!

Swann-Morton

Swann-Morton Limited, Penn Works
Owlerton Green, Sheffield S6 2BJ
England
Tel: (0742) 344231
Fax: (0742) 314966
Telex: 547538


MEDICAL STATISTICS ON MICROCOMPUTERS
R A BROWN
J SWANSON BECK
JOURNAL OF CLINICAL PATHOLOGY
BMJ

How is no longer a problem – but there's still which and why

The microcomputer revolution has made powerful machines and highly complex programs generally available. This means that users of statistical techniques need no longer be concerned with the arithmetical and algebraic details – the software will take care of all that. What is vital, however, is to understand the ideas and the basic principles of statistical analysis. In *Medical Statistics on Microcomputers* R A Brown and J Swanson Beck show how to get the best use out of microcomputers when analysing data, particularly in the pathology laboratory. They explain the rational basis of various widely applicable statistical methods and also indicate their limitations so that you can make an informed choice. Chapters include:

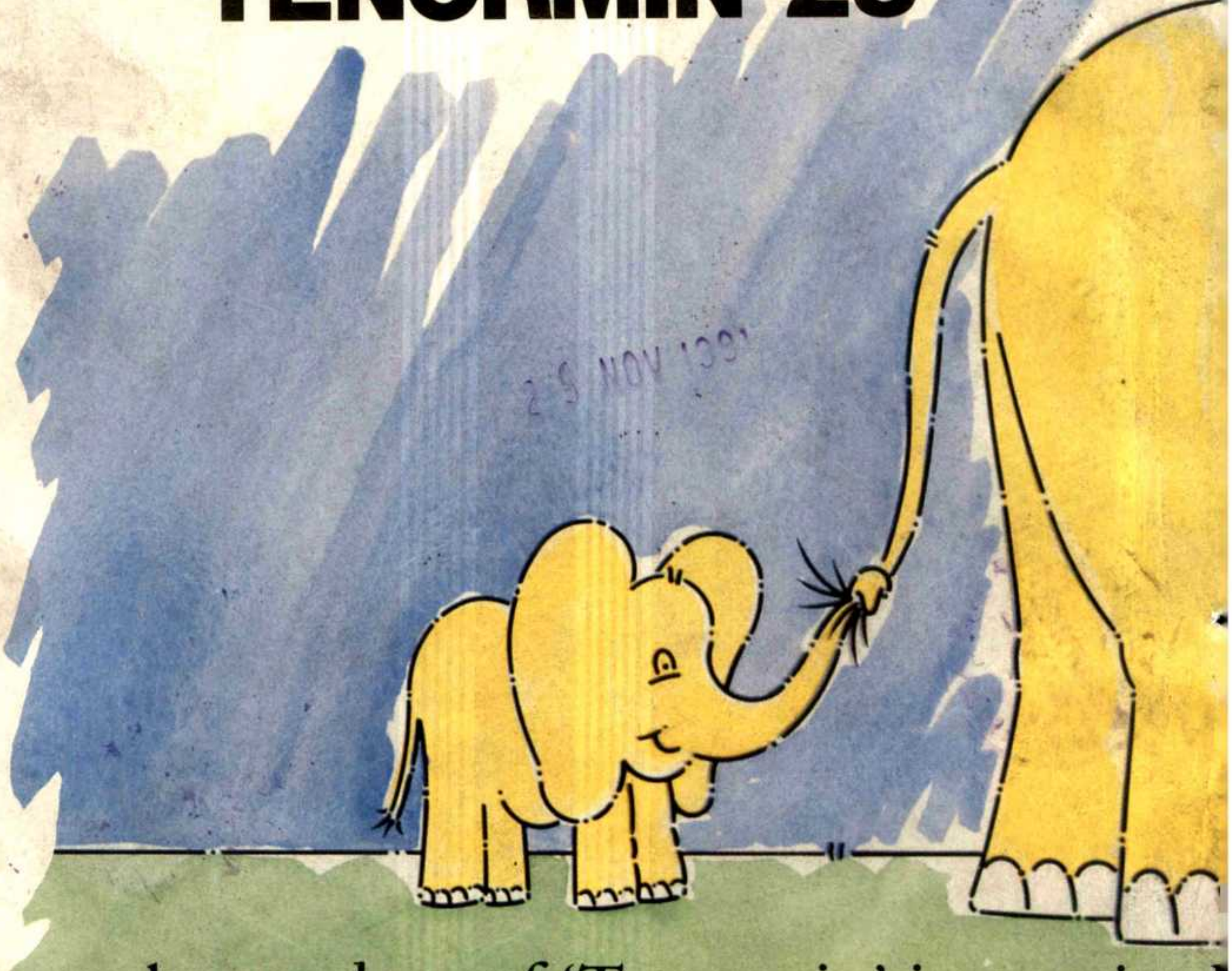
- Data handling
- Analysis of data from one or two groups
- Comparison of several groups
- Analysis of categorical data
- Statistical methods for diagnostic tests.

UK £8.95; Abroad £10.50
BMA members: £8.45 or £10.00
including postage by air abroad

Available from: BRITISH MEDICAL JOURNAL, PO BOX 295, LONDON WC1H 9TE, *any leading bookseller or the BMJ/BMA bookshop in BMA House.*

Please enclose payment with order, or send us full details of your MASTERCARD, VISA or AMERICAN EXPRESS credit card.

DON'T FORGET!
TENORMIN 25



2 9 NOV 199

When a lower dose of 'Tenormin' is required – in renal impairment

Tenormin 25
atenolol 25mg

Prescribing notes for *Tenormin* atenolol 100mg *Tenormin* LS atenolol 50mg *Tenormin* 25 atenolol 25mg

Consult data sheet before prescribing.

USE: Hypertension, angina prophylaxis.

PRESENTATION: Tablets for oral administration containing atenolol 100mg ('Tenormin'), 50mg ('Tenormin' LS) or 25mg ('Tenormin' 25).

DOSAGE AND ADMINISTRATION: Hypertension: Tenormin' – one daily (some patients may respond adequately to 'Tenormin' low strength (LS)); 'Tenormin' LS – one daily; 'Tenormin' 25 - see renal failure. **Angina Prophylaxis:** 'Tenormin' – one daily; 'Tenormin' LS – two daily in a single or divided dose. **Children:** 'Tenormin', 'Tenormin' LS and 'Tenormin' 25 are not recommended for use in children. **Elderly Patients:** Dosage requirements may be lower in elderly patients. **Renal Failure:** For patients with a creatinine clearance of 15-35ml/min/1.73m^2 the oral dose should be 50mg daily. Patients with a creatinine clearance of <15ml/min/1.73m^2 should be given one 'Tenormin' 25 daily or one 'Tenormin' LS on alternate days.

CONTRAINDICATIONS: 2nd or 3rd degree heart block, cardiogenic shock.

PRECAUTIONS: Poor cardiac reserve – avoid in overt heart failure. Bradycardia, renal failure (see above), anaesthesia, pregnancy. Caution in patients with reversible obstructive airways disease – do not u unless there are compelling clinical reasons to do so. Atenolol modifies the tachycardia of hypoglycaem Co-administration with verapamil or Class I antidysrhythmic agents. Withdrawal of clonidine. Withdrawa beta-blocking drugs should be gradual in patients with ischaemic heart disease.

SIDE EFFECTS: Coldness of extremities, bradycardia and muscular fatigue may occur. Sleep disturba rarely seen. Skin rashes and dry eyes have been reported with beta-blockers – consider discontinuanc they occur.

PRODUCT LICENCE NUMBERS AND BASIC NHS COSTS: 'Tenormin' (29/0122), 28 tablets (£6.98. 'Tenormin' LS (29/0086), 28 tablets (OP) £5.49, 'Tenormin' 25 (29/0218), 28 tablets (OP) £4.

'Tenormin', 'Tenormin' LS and 'Tenormin' 25 are trademarks.

Further information is available from
Stuart Pharmaceuticals, King's Court,
Water Lane, Wilmslow, Cheshire SK9 5AZ.

STUA
May '91/2

OCTOBER 1991 VOL 66 No 4

Acc 12 2/93

UCM

BRITISH HEART JOURNAL

LIBRARY

In association with the British Cardiac Society

Editorial

261 Using skeletal muscle to assist the heart *T L Hooper, L W Stephenson*

Review

264 Vascular tone in heart failure: the neuroendocrine-therapeutic interface *J G F Cleland, C M Oakley*

Original articles

268 Relation between cyclic variation in echo amplitude and segmental contraction in normal and abnormal hearts *D A Lythall, R B Logan-Sinclair, C J D Ilsley, S S Kushwaha, M H Yacoub, D G Gibson*

277 Responsiveness of raised pulmonary vascular resistance to oxygen assessed by pulsed Doppler echocardiography *M Vogel, J Weil, H Stern, K Bühlmeyer*

281 Transoesophageal echocardiographic assessment of fixed subaortic obstruction in children *J P Gnanapragasam, A B Houston, W B Doig, M P G Jamieson, J C S Pollock*

285 Assessment of right and left ventricular function in terms of force development with gestational age in the normal human fetus *M St John Sutton, T Gill, T Plappert, D H Saltzman, P Doubilet*

290 Non-invasive measurement of the regurgitant fraction by pulsed Doppler echocardiography in isolated pure mitral regurgitation *C Tribouilloy, W F Shen, M A Slama, H Dufossé, D Choquet, A Marek, J-P Lesbre*

295 Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease *P H Groves, N P Lewis, S Ikram, R Maire, R J C Hall*

302 Role of transoesophageal echocardiography in evaluation of cardiogenic embolism *I W Black, A P Hopkins, L C L Lee, B M Jacobson, W F Walsh*

308 DiGeorge syndrome with isolated aortic coarctation and isolated ventricular septal defect in three sibs with a 22q11 deletion of maternal origin *D I Wilson, I E Cross, J A Goodship, S Coulthard, A H Carey, P J Scambler, H H Bain, A S Hunter, P E Carter, J Burn*

313 Silent ischaemia in diabetic men with autonomic neuropathy *J J O'Sullivan, R M Conroy, K MacDonald, T J McKenna, B J Maurer*

316 Myocardial ischaemia and ventricular arrhythmias precipitated by physiological concentrations of adrenaline in patients with coronary heart disease *A J McCance, J C Forfar*

Case report

320 Paradoxical embolisation of a catheter fragment to a coronary artery in an infant with congenital heart disease *H S Klys, A P Salmon, J V De Giovanni*

Views from the past

322 John Fothergill and angina pectoris *W L Proudfit*

British Cardiac Society

325 Coronary angioplasty in the United Kingdom *Report of a working party of the British Cardiac Society*

301 **Plants in cardiology**

307 **Obituary: Eirian Williams**

332 **British Cardiac Society newsletter**

332 **Notices**

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

BRITISH HEART JOURNAL

In association with the British Cardiac Society
A Registered Charity

Editor: Dennis Krikler
Assistant Editors: Kim Fox, Peter Mills
Technical Editor: Jane Dawson
Editorial Assistant: Anne Oliver
Editorial Secretary: Maureen Emerson
Associate Editor: M J Davies
Statistical Adviser: Stephen J W Evans

EDITORIAL COMMITTEE
Roger M Boyle
Stuart M Cobbe
Keith Dawkins
John L Gibbs
Roger Hall
Alan B Houston
Stewart Hunter
Barry R Keeton
Michael Marmot
R Gordon Murray
John Sanderson
Tom Treasure
David E Ward
Peter Wilde
Editor: *BMJ*
Editor: *Cardiovascular Research*

NOTICE TO CONTRIBUTORS

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). **Authors are asked to complete a copy of the checklist provided (1991;65:59–60 (January issue)) when submitting their manuscripts for publication.** The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with wide margins.)

ETHICAL STANDARDS

Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

CASE REPORTS should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

ABBREVIATIONS should *not* be used in the text, except for mathematical calculations and units of measurement.

REFERENCES must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

UNITS OF MEASUREMENT

All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

TABLES must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

ILLUSTRATIONS (for general requirements, please refer to *Br Heart J* 1984;51:1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible.

Echocardiograms: All unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

COPYRIGHT PERMISSION to reproduce material published elsewhere must be obtained in writing and acknowledged in the manuscript.

PROOFS of articles accepted for publication will be sent for the author's approval. Proof corrections should be kept to a minimum.

NOTICE TO SUBSCRIBERS

British Heart Journal is published monthly. The annual subscription rates are £126.00 inland and £136.00 overseas (USA $230·00). Combined rate: *British Heart Journal* and *Cardiovascular Research* £238.00 inland and £255.00 overseas (USA $443·00). Orders should be sent to The Subscription Manager, *British Heart Journal*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. (For the convenience of readers in the USA subscription orders ($230·00) with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) **All copies are despatched by air-speed.** First class rates available on request.

COPYRIGHT © 1991 by the *British Heart Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the *British Heart Journal*.

ISSN 0007–0769

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR and
printed in England by
Eyre & Spottiswoode Ltd,
London and Margate

Second class postage paid, Rahway NJ Postmaster: send address changes to: British Heart Journal c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

Br Heart J 1991;66:261-3

BRITISH
HEART
JOURNAL

Acc 12 7/93

Editorial

Using skeletal muscle to assist the heart

The concept of using the contractile power of skeletal muscle to assist the heart was first proposed in 1959,[1] but further work was initially discouraged by the finding that skeletal muscle fatigued rapidly if subjected to the continuous work necessary for cardiac assistance. An important development was the demonstration that cross-innervation of a fast-twitch muscle with the motor nerve of a slow-contracting muscle altered its functional characteristics to resemble the slow type muscle, which is more fatigue-resistent.[2] Later, Salmons and Vrbova discovered that the same phenomenon could be achieved by subjecting a fast muscle to chronic, low frequency electrical stimulation.[3] The possibility that this phenomenon might be exploited to adapt skeletal muscle for cardiac-type work was first suggested in 1981[4-7] and resulted in a considerable revival of interest in the subject.

Transformation

Muscle transformation of this type is characterised by biochemical and ultrastructural adjustments. There is a transition from fast myosin isoforms to those found in slow muscle fibres,[8 9] and this, together with changes in calcium transport ATPase[10] and calcium-binding proteins,[11] results in reduced contractile speed of the muscle. Simultaneously, there is a shift in metabolism in favour of the oxidative rather than the glycolytic pathways,[12 13] and ultrastructural reorganisation occurs, including a considerable increase in capillary density[14] and mitochondrial volume fraction,[13 15] and a reduction in sarcoplasmic reticulum.[15] Studies with ^{31}P-nuclear magnetic resonance confirmed that the decline in phosphocreatine and accumulation of inorganic phosphate, which characterise muscle fatigue, occur to a smaller extent in conditioned muscle.[16] This considerable increase in the capacity for oxidative phosphorylation rivals that of cardiac muscle, and, together with changes in the bioenergetics of muscle contraction, results in more efficient coupling between the development and maintenance of tension and oxygen consumption.[17] With appropriate electrical conditioning muscle transformation can be accomplished in six to eight weeks[8] and is associated with a greatly increased resistance to fatigue.

Use of the latissimus dorsi

Attempts to provide myocardial support with skeletal muscle have focused mainly on the use of the latissimus dorsi muscle, which offers certain advantages suited to a cardiac assist role. Being supplied primarily by a single neurovascular pedicle, the muscle is easily mobilised and transposed within the chest without incurring significant impairment of shoulder function.[18] In addition, the muscle has a bulk comparable with that of the left ventricle,[19] and because skeletal muscle is capable of more work per unit weight than cardiac muscle,[20] a single latissimus dorsi has the potential for assuming a major part of the workload of the left ventricle.

But after division of collateral blood vessels to the latissimus dorsi during its mobilisation from the chest wall, the distal half of the muscle becomes ischaemic. A three week vascular delay period, before chronic stimulation of the muscle, allows recovery of normal resting and exercise-induced blood flow.[19 21 22] It has also been emphasised that, to generate cardiac-type work from skeletal muscle, a burst-pattern of stimulation of the motor nerve is necessary to induce mechanical summation of contractile force.[23] Sophisticated, programmable pacemakers are now available that can sense the electrocardiogram and deliver an appropriately timed burst stimulus to the motor nerve of the muscle.[24]

Cardiomyoplasty

Attempts to use skeletal muscle work to support cardiac function have become polarised into two main approaches. One is in the form of a cardiomyoplasty, in which the muscle is wrapped around the heart, such that it may directly augment myocardial contraction. The alternative method provides indirect assistance, often with aortic counterpulsation techniques. In the cardiomyoplasty procedure, the latissimus dorsi muscle is stimulated to contract synchronously with systole. This operation was first performed experimentally in 1959 with diaphragm muscle,[1] and later, in 1968, using latissimus dorsi.[25] It was applied for the first time clinically in 1985 to provide functional replacement of a large ventricular defect created by excision of a benign cardiac tumour.[26] Subsequently, the technique was used for repair after aneurysmectomy or for simple reinforcement of damaged, hypokinetic myocardium.[27-29] Enthusiasm is such that over 100 cardiomyoplasties have now been performed clinically (unpublished data).

While many patients have experienced an improvement in symptoms of heart failure, it has proved difficult to demonstrate a consistent haemodynamic improvement in terms of reduction of cardiac filling pressures or increases in cardiac output or ejection fraction.[28 29] Attempts to document such changes in animals undergoing cardiomyoplasty have also provided conflicting results.[30-32] This may be related to the configuration of the muscle wrap, which encompasses a large radius of curvature, and thus (according to Laplace's Law) acts at a mechanical disadvantage when the aim is to develop a significant pressure change within the left ventricle.[33] In addition, electrical conditioning of skeletal muscle to a fatigue-resistant form reduces both the power output and shortening velocity; this will further prejudice the maximum tension developed by the muscle during the systolic interval.[33] It may be that symptomatic improvement after cardiomyoplasty derives in part from a more passive role of the muscle flap, which prevents further dilatation of the heart and perhaps reduces myocardial wall stress by virtue of an effective increase in wall thickness.[33,34]

Though the precise role of cardiomyoplasty is currently uncertain, an important report has recently appeared from São Paulo, Brazil.[35] Of 29 patients with dilated cardiomyopathy, 13 underwent cardiomyoplasty and 16, who refused the procedure, continued to receive medical treatment. Although this was not a randomised trial, the two study groups were comparable in other respects. In 10 of the 13 patients functional state (New York Heart Association classification) improved after cardiomyoplasty, and mean left ventricular ejection fraction increased by about 30%. However, of particular interest was the finding of improved 18-month actuarial survival in the cardiomyoplasty group compared with those treated medically (80% *v* 31%). This is the first study to suggest such a survival advantage.

Auxiliary pumping chambers

The alternative avenue of investigation has been the formation of separate skeletal muscle pouches or ventricles (SMVs), which function as auxiliary pumping chambers. They are constructed by wrapping the mobilised latissimus dorsi muscle around a conical Teflon stent that is later removed to create the pouch cavity. SMVs connected to an implantable mock-circulation device, capable of simulating predetermined conditions of preload and afterload, generated continuous stroke work intermediate between that of the left and right ventricles for several weeks.[36] These results were later confirmed when SMVs were placed in a dog's circulation via the thoracic aorta and stimulated in synchrony with diastole to create aortic counterpulsation.[37] One dog is alive a year after such a procedure, with the SMV continuing to provide effective aortic counterpulsation.[38] The counterpulsation mode of assist had been chosen because the compliance of SMVs necessitated high preloads to generate optimal power output. However, with improvements in SMV design, based on previous laboratory experience and the use of mathematical models,[39] the compliance of these pouches has been improved to the extent that SMVs have successfully supported or replaced right ventricular function at near physiological preloads in short term experiments.[40,41] Continued modifications in design have more recently enabled SMVs, in acute experiments, to generate a level of work greater than that of the left ventricle at low preloads.[42] Thromboembolism and SMV rupture are among the major problems still to be overcome before this form of assist is applied clinically.

Other counterpulsation techniques

Other means for generating aortic diastolic counterpulsation powered by skeletal muscle have been suggested. The latissimus dorsi can be wrapped around the thoracic aorta, providing direct compression during stimulation, and this has resulted in circulatory assistance during short term studies.[43] This method has the advantage that thromboembolic complications are avoided because foreign surfaces do not come into direct contact with blood. One disadvantage is that the degree of assist is limited by the volume of blood that can be displaced using this configuration. One answer is to enlarge the diameter of the aorta with a patch, so as to augment volume displacement.[43]

An alternative method for generating counterpulsation has been to exploit the concept of the intra-aortic balloon pump, already a widely accepted form of clinical cardiac assist. A counterpulsation system powered by skeletal muscle has been devised. It consists of a cylindrical housing containing a silicone bladder that is anastomosed to the aorta. The inner bladder is displaced pneumatically by compression of a bulb placed either within an SMV[44] or beneath the intact latissimus dorsi muscle.[45] During muscle stimulation aortic diastolic pressure augmentation has been effective for up to several weeks. A major disadvantage of this device is that the vehicle used for transmitting pressure changes between the two chambers, whether gas or liquid, tends to leak from the system, thereby impairing the efficiency.

While conditioned skeletal muscle currently offers a realistic means of providing functional support for the failing myocardium, more research is required to define the optimal mode of assist for different patient subgroups. The mechanism by which cardiomyoplasty augments cardiac function is unclear, though an improvement in symptoms after the procedure is being increasingly reported, particularly in patients with dilated cardiomyopathy. SMVs, on the other hand, have the potential to replace left or right ventricular function, and have pumped effectively in the canine circulation for more than a year. With continued improvements in SMV design the future for this mode of support is promising. The efficacy of some other forms of circulatory support by skeletal muscle remains to be elucidated.

TIMOTHY L HOOPER
LARRY W STEPHENSON

Division of Cardiothoracic Surgery,
Wayne State University,
Harper Professional Building, Suite 228,
Detroit, Michigan 48201, USA

1 Kantrowitz A, McKinnon W. The experimental use of the diaphragm as an auxiliary myocardium *Surg Forum* 1959,9:266-8.
2 Buller AJ, Eccles JC, Eccles RM. Interactions between motoneurones and muscles in respect of the characteristic speeds of their responses *J Physiol (Lond)* 1960;150:417-39.
3 Salmons S, Vrbova G. The influence of activity on some contractile characteristics of mammalian fast and slow muscles. *J Physiol (Lond)* 1969;201 535-49
4 Macoviak JA, Stephenson LW, Kelly AM, Likoff MJ, Reichek N, Edmunds LH Partial replacement of the right ventricle with a synchronously contracting diaphragmatic skeletal muscle autograft. *Artif Organs* 1981;5 (suppl):550-5.
5 Macoviak JA, Stephenson LW, Alavi A, Kelly AM, Edmunds LH. Effects of electrical stimulation on diaphragmatic muscle used to enlarge the right ventricle. *Surgery* 1981,90.271-7.
6 Macoviak JA, Stephenson LW, Armenti F, *et al* Electrical conditioning of in situ skeletal muscle for replacement of the myocardium. *J Surg Res* 1982,32 429-39.
7 Armenti FR, Bitto T, Macoviak JA, *et al*. Transformation of skeletal muscle for cardiac replacement *Surg Forum* 1984,35.258-60.
8 Sreter FA, Gergely J, Salmons S, Romanul F. Synthesis by fast muscle of myosin light chains characteristic of slow muscle in response to long-term stimulation. *Nature* 1973,241.17-9.
9 Brown WE, Salmons S, Whalen RG. The sequential replacement of myosin sub-unit isoforms during muscle type transformation induced by long-term electrical stimulation *J Biol Chem* 1983;258.14686-92.
10 Heilmann C, Pette D Molecular transformations in sarcoplasmic reticulum of fast-twitch muscle by electro-stimulation. *Eur J Biochem* 1979;93·437-46.
11 Leberer E, Seedorf U, Pette D. Neural control of gene expression in skeletal muscle. Calcium-sequestering proteins in developing and chronically stimulated rabbit skeletal muscles *Biochem J* 1986;239:295-300.
12 Pette D, Muller W, Leisner E, Vrbova G. Time-dependent effects on contractile properties, fibre population, myosin light chains and enzymes of energy metabolism, in intermittently and continuously stimulated fast twitch muscles of the rabbit. *Pflugers Arch* 1976,364:103-12.
13 Reichman H, Hoppeler H, Mathieu-Costello O, *et al*. Biochemical and ultrastructural changes of skeletal muscle mitochondria after chronic electrical stimulation in rabbits *Pflugers Arch* 1985,404·1-9.

14 Brown MD, Cotter MA, Hudlicka O, Vrbova G. The effects of different patterns of muscle activity on capillary density, mechanical properties, and structure of slow and fast rabbit muscles *Pflugers Arch* 1976,361:241-50.

15 Eisenburg BR, Salmons S. Reorganisation of subcellular structure in muscle undergoing fast to slow type transformation. a stereological study. *Cell Tissue Res* 1981;220:449-71.

16 Acker MA, Clark BJ, Subramanian H, *et al.* In vivo P-NMR spectroscopy of electrically conditioned skeletal muscle. *Circulation* [abstract] 1986;74 (suppl II)·II.415.

17 Acker MA, Anderson WA, Hammond RL, *et al.* Oxygen consumption of chronically stimulated skeletal muscle. *J Thorac Cardiovasc Surg* 1987;94·702-9

18 Laitung JKG, Peck F Shoulder function following loss of the latissimus dorsi muscle. *Br J Plast Surg* 1985;38.375-9.

19 Mannion JD, Hammond RL, Stephenson LW Hydraulic pouches of canine latissimus dorsi· potential for left ventricular assistance. *J Thorac Cardiovasc Surg* 1986,91:534-44.

20 Salmons S, Jarvis JC. The working capacity of skeletal muscle transformed for use in a cardiac assist role. In Chiu RC-J, Bourgeois IM, eds. *Transformed skeletal muscle for cardiac assist and repair*. New York: Futura Publishing Co, 1990·89-104.

21 Mannion JD, Velchik MA, Acker M, *et al.* Transmural blood flow of multilayered latissimus dorsi skeletal muscle ventricles during circulatory assistance. *Trans Am Soc Artif Intern Organs* 1986,32 454-60

22 Mannion JD, Velchick M, Hammond RL, *et al* Effects of collateral blood vessel ligation and electrical conditioning on blood flow in dog latissimus dorsi *J Surg Res* 1989,47·332-40.

23 Dewer ML, Drinkwater DC, Wittnich C, Chiu RC-J. Sychronously stimulated skeletal muscle graft for myocardial repair. *J Thorac Cardiovasc Surg* 1984,87 325-31.

24 Acker MA, Anderson WA, Hammond RL, *et al.* Skeletal muscle ventricles in circulation. One to eleven weeks experience. *J Thorac Cardiovasc Surg* 1987,94·163-74

25 Hume WI Construction of a functioning accessory myocardium. *Trans Southern Surg Assoc* 1968;79 200-2.

26 Carpentier A, Chachques JC. Myocardial substitution with a stimulated skeletal muscle: first successful clinical case. *Lancet* 1985,i:1267.

27 Chachques JC, Grandjean PA, Pfeffer TA, *et al* Cardiac assistance by atrial or ventriclular cardiomyoplasty. *J Heart Transplant* 1990;9·239-51

28 Hagege AA, Desnos M, Chachques JC, *et al.* Preliminary report: follow-up after dynamic cardiomyoplasty *Lancet* 1990,335:1122-4.

29 Magovern GJ, Park SB, Kao RL, Christlieb IY, Magovern GJ. Dynamic cardiomyoplasty in patients. *J Heart Transplant* 1990,9.258-63

30 Chachques JC, Grandjean P, Schwartz K, *et al.* Effect of latissimus dorsi dynamic cardiomyoplasty on ventricular function *Circulation* 1988,78 (suppl III) III.203-16.

31 Chagas AC, Moreira LF, Da Luz PL, *et al.* Stimulated preconditioned skeletal muscle cardiomyoplasty. *Circulation* 1989;80 (suppl III) III.202-8.

32 Anderson WA, Andersen JS, Acker MA, *et al* Skeletal muscle grafts applied to the heart. A word of caution. *Circulation* 1988,78 (suppl III)·III.180-90

33 Salmons S, Jarvis JC. Cardiomyoplasty· the basic issues. *Cardiac Chronicle* 1990;4:1-7.

34 Lee KF, Dyke CM, Wechsler AS. Theoretical considerations in the use of dynamic cardiomyoplasty to treat dilated cardiomyopathy *J Cardiac Surg* 1991,6 119-23.

35 Moreira LFP, Seferian P, Edimar A, *et al.* Survival improvement with dynamic cardiomyoplasty in patients with dilated cardiomyopathy. *Circulation* [abstract] 1990,82 (suppl III)·III.713.

36 Acker MA, Hammond RL, Mannion JD, Salmons S, Stephenson LW. Skeletal muscle as a potential power source for a cardiovascular pump assessment in vivo. *Science* 1987,236.324-7.

37 Mannion JD, Acker MA, Hammond RL, Faltemeyer W, Duckett S, Stephenson LW. Power output of skeletal muscle ventricles in circulation short-term studies. *Circulation* 1987,76.155-62

38 Anderson DR, Pochettino A, Hammond RL, *et al* Skeletal muscle ventricles in circulation as aortic diastolic counterpulsators twelve-month update *J Cardiac Surg* 1990;5 199-203

39 Bridges CR, Andersen JS, Anderson WA, *et al.* Skeletal muscle ventricles. preliminary results and theoretical design considerations. In. Reichart B, ed. *Recent advances in cardiovascular surgery*. Munich. Verlag RS Schultz, 1989.182-202.

40 Bridges CR, Woodford E, Mora G, Anderson DR, Stephenson LW, Norwood WI Use of skeletal muscle power to augment the pulmonary circulation *Surg Forum* 1990;41·267-71.

41 Bridges CR, Hammond RL, Dimeo F, Anderson WA, Stephenson LW Functional right-heart replacement with skeletal muscle ventricles. *Circulation* 1989,80 (suppl III):III 183-91

42 Pochettino A, Spanta A, Hammond RL, *et al.* Skeletal muscle ventricles for total heart replacement. *Ann Surg* 1990,212:345-52

43 Chachques JC, Grandjean PA, Fischer EI, *et al* Dynamic aortomyoplasty to assist left ventricular failure. *Ann Thorac Surg* 1990;49:225-30

44 Anderson WA, Bridges CR, Chin AJ, *et al.* Long-term neurostimulation of skeletal muscle its potential for a tether-free biologic cardiac assist device. *PACE* 1988,11:2128-34

45 Li CM, Hill A, Colson M, Desrosiers C, Chiu R C-J Implantable rate-responsive counterpulsation assist system *Ann Thorac Surg* 1990,49 356-62.

Br Heart J 1991;*66*:264–7

REVIEW

Vascular tone in heart failure: the neuroendocrine-therapeutic interface

John G F Cleland, Celia M Oakley

Impaired cardiac function is of course the primary problem in heart failure, but it is also the stimulus to activation of several integrated neuroendocrine systems. Activation of these neuroendocrine systems at first seems to have important beneficial effects for the failing circulation—maintaining cardiac output, blood pressure, blood flow to essential organs, and the glomerular filtration rate. Prolonged or extreme neuroendocrine activation, however, may prove deleterious.

The advent of effective diuretics had a tremendous impact on the management of patients with heart failure. Then, in the absence of a cure for the primary problem, thoughts returned to agents that either increased the force of myocardial contraction (inotropic agents) or reduced the load on the failing heart (vasodilator agents). Both modes of treatment have proved effective in improving haemodynamic function in the short term. Neither therapeutic intervention has yet been established as having beneficial effects for long term treatment of heart failure.

A fourth group of agents was added to the treatment of heart failure in the 1980s. The angiotensin converting enzyme (ACE) inhibitors have showed not only their ability to improve symptoms and exercise performance, but also to reduce mortality and possibly slow the rate of decline in ventricular function. In the 1990s their use is certainly going to increase. These agents are more than just another group of vasodilator agents. Their effects on neuroendocrine activity seem to be integral to their success. A review of the interaction between neuroendocrine variables and vasodilator therapy is timely.

Historical perspectives

Before the 1940s theories on the nature of the circulatory disorder in heart failure abounded, but the means of treating the condition were limited. The advent of cardiac catheterisation, of methods of measuring regional blood flow, and, finally, of non-invasive measures of cardiovascular function has contributed to better understanding of the interplay between the failing heart and the abnormal circulation that it still supports.

The introduction of mercurial diuretics in the 1920s, thiazides in the 1950s, and loop diuretics in the 1960s all made substantial contributions to the alleviation of symptoms while leading indirectly to some deleterious haemodynamic and neuroendocrine effects.

The relation between cardiac output and venous pressure in heart failure was described at the Hammersmith Hospital in the 1940s, and Wood recognised that increased systemic vasoconstriction was one of the hallmarks of heart failure.[1 2] These ideas were brought together by Braunwald in the 1960s, who integrated the concepts of altered pre-load, after-load, and myocardial contractility and promoted the theoretical rationale for vasodilator therapy for heart failure.[3]

However, the concept of reducing vascular tone in the treatment of heart failure is much older. Osler (1892) used nitroglycerine[4] and Savill (1936) suggested sympathectomy[5] as a treatment for intractable heart failure. These ideas gained substance in the 1950s, with the use of ganglion blocking agents[6] and nitrates.[7] Since then, nitrates have achieved a lasting place in the management of pulmonary oedema. The use of phentolamine in the 1970s ushered in the "modern" era of vasodilator therapy.[8] However, despite all the theoretical considerations, until the appearance of ACE inhibitors in the 1980s, vasodilator agents achieved no firm practical role in the management of chronic heart failure.

Neuroendocrine consequences of heart failure

The circulation responds both to changes in volume and to changes in pressure. Those reflexes which depend on pressure receptors (that is, carotid, aortic arch, and renal) seem to work fairly normally in heart failure,[9 10] with reduction in arterial wall tension activating the sympathetic nervous and renin-angiotensin-aldosterone systems. Though such reflexes may be slightly blunted they work in a directionally normal sense.

In contrast, volume dependent reflexes (that is, of the atria and great veins) seem to be markedly blunted or directionally abnormal. The diuresis that can be elicited by atrial distention is reduced. Although atrial natriuretic peptide is increased[11] its renal effects are considerably reduced in heart failure. Plasma concentrations of arginine vasopressin, which would normally be suppressed during atrial distention, are increased.

Animal models of heart failure suggest that initial activation of the sympathetic nervous

Department of Medicine (Clinical Cardiology), Royal Postgraduate Medical School, Hammersmith Hospital, London
J G F Cleland
C M Oakley

Correspondence to
Dr John G F Cleland,
Department of Medicine,
Clinical Cardiology Unit,
Hammersmith Hospital, Du Cane Road, London
W12 0NN

and renin-angiotensin systems results in fluid retention and vasoconstriction.[12] If the primary myocardial insult is not too severe, fluid retension causes blood volume expansion with a restoration of arterial pressure, and as this occurs activation of the neuroendocrine systems wanes. This is consistent with observations in patients developing heart failure after myocardial infarction.[13] However, if the cardiac insult is severe enough haemodynamic equilibrium cannot be achieved. This may manifest itself in several ways; cardiogenic shock will result from an excessive fall in stroke output or pulmonary oedema from an excessive rise in left atrial pressure. Most patients with chronic heart failure are already receiving diuretics which prevent the patient from attaining haemodynamic equilibrium; therefore activation of vasoconstrictor neuroendocrine systems is maintained. Diuretics, by reversing fluid retention, reveal the underlying activation of the renin-angiotensin system. High plasma concentrations of renin, angiotensin II, noradrenaline, and atrial natriuretic peptide are also important and indicate a poor prognosis.[14 15] High concentrations of catecholamine and angiotensin II[16] may be directly cardiotoxic as well as adding to a downward spiral of increasing vascular resistance, neuroendocrine activation, and deteriorating haemodynamic function. However, it is not certain whether neuroendocrine activation itself makes a contribution to increasing mortality or is just a marker of severity. The demonstration that normal concentrations of plasma renin with high sympathetic activity may be exchanged for the converse by diuretics[17] illustrates the absence of any simple relation between neuroendocrine activation and prognosis.

"Conventional" vasodilators

Despite many trials on vasodilators there is little evidence that they are effective in improving symptoms and exercise performance in chronic heart failure.[18-20] Although the combination of nitrates and hydralazine did reduce mortality in one study the effect was modest.[21] Some studies have purported to show benefit with each of these agents, but all are flawed because of inadequate control data, changes in diuretic dose, or misrepresentation of results.[22 23] There is now ample evidence that "conventional" vasodilators are inferior to ACE inhibitors, and of the reasons for this.

As heart failure develops, vascular resistance increases; but this does not happen equally in all vascular beds. Blood flow to the limbs and brain is reduced at rest in more severe cases only, whereas renal blood flow declines from an early stage. During exercise blood flow to the exercising muscle is reduced—and flow to the kidney is reduced even more. Conventional vasodilators are not "intelligent". They reduce vascular resistance, but not selectively. They increase blood flow to non-essential organs, such as the skin, and do not increase the use of oxygen by the limbs during exercise despite increasing limb blood flow.[24 25] Thus blood seems to be shunted past metabolically active muscle.

Management of the patient with acute pulmonary oedema according to the classic principles of reduction of pre and after load is effective, but these same haemodynamic concepts may be less appropriate in the management of chronic heart failure. Changes in skeletal muscle related to deconditioning,[26] intracellular deficits of potassium,[27] or excesses of sodium[27] may also be important therapeutic targets in chronic heart failure, when the underlying cardiac abnormality itself cannot be corrected.

Clearly there is a big difference between the regional distribution of the cardiac output "driven" by the heart and output "led" by reducing the vascular resistance.

Tolerance to vasodilator agents: role of neuroendocrine activation

Tolerance to vasodilators may be caused by metabolic changes in the vascular wall, as in the case of nitrates, leading to a loss of effect on vascular smooth muscle. In many instances, however, neuroendocrine and metabolic (mal)adaptations may be even more important, or the sole cause.

Administration of the powerful vasodilators minoxidil and diazoxide to patients with heart failure results in immediate beneficial haemodynamic effects, but gross fluid retention rapidly supervenes.[28] A similar phenomenon, milder in degree, probably occurs with other arteriolar dilators, due to a fall in arterial pressure, and hence renal perfusion pressure. Associated increases in the activities of the sympathetic nervous and renin-angiotensin-aldosterone systems can further exacerbate renal sodium retention.[28-30] Increasing the dose of diuretic to reverse fluid retention leads to greater neuroendocrine activation, which will further reverse the vasodilatation. Increases in angiotensin II and the fall in perfusion pressure can cause a paradoxical fall in renal blood flow,[31] and create a vicious cycle of declining renal function and increasing diuretic requirements. Agents that reduce atrial pressure are likely to exacerbate fluid retention still further by reducing atrial natriuretic peptide—though patients with heart failure seem less responsive to atrial peptide, it is not entirely devoid of action.

The development of tolerance means that no true test of the therapeutic effects of chronic vasodilation in heart failure can be made with "conventional" vasodilators. Attempts have been made to reverse the effects of neuroendocrine activation induced by prazosin using spironolactone with unconfirmed success.[32] Combining prazosin and captopril does not prevent fluid retention or improve the clinical response.[33] The combination of a vasodilator with an atrial peptidase inhibitor is currently being evaluated.

Angiotensin converting enzyme inhibitors

ACE inhibitors have proven salutary effects on the symptoms and signs of heart failure, improve the "metabolic profile" of the patient, increase renal blood flow, may reduce arrhythmias and progressive ventricular dysfunction, and improve survival.[34-36] Compared with "conventional" vasodilators the effects of ACE inhibitors on cardiac output are generally modest: their comparative therapeutic benefits are not.[17 37] Studies that suggest that ACE inhibitors exert their benefits by increasing effective oxygen delivery to the exercising limb, in contrast with "conventional" vasodilators, are flawed in their argument.[38] Association does not equal causation. Increased exercise performance would be expected to lead to a more pronounced reduction in vascular resistance in response to the accumulation of vasodilating waste products in exercising muscle, which in turn will lead to increased blood flow. Improvements in blood flow during chronic therapy probably owe more to changes in vessel wall composition and the capacity of the vessel valve to respond to vasodilator stimuli rather than to simple direct vasodilatation.

Neuroendocrine effects

ACE inhibitors exert most of their effects by reducing angiotensin II. The inhibition of bradykinin stimulation and the effects on prostaglandins are of uncertain clinical significance. The immediate response to an ACE inhibitor is a reduction in the plasma concentrations of angiotensin II, aldosterone, noradrenaline, and atrial natriuretic peptide.[39 40] Adrenaline and arginine vasopressin show little change unless hypotension is profound.[41]

Longer term inhibition of ACE results in continued supression of angiotensin II, aldosterone, and noradrenaline plus a decline in arginine vasopressin.[35 36] Increases in renin and angiotensin II activity in response to diuretics, standing, and exercise are prevented.[42] Suppression of aldosterone declines with time, a result of a rise in serum potassium concentration, which stimulates aldosterone secretion. This is a useful safeguard against severe hyperkalaemia during ACE inhibition. Plasma noradrenaline is suppressed in the supine position, but increases in response to standing, a normal reflex usually absent in patients with heart failure.[42] The response to exercise is less clear, but for the same level of exercise sympathetic activation may be less. Arginine vasopressin is also reduced in the supine position but in response to diuretics, standing, and exercise, rises to pre-treatment concentrations. Atrial natriuretic peptide may also rise to pre-treatment concentrations despite a continued fall in atrial pressure.[43]

Metabolic effects

ACE inhibitors share some of the problems of other vasodilators, namely hypotension and sodium retention when treatment starts.[39 44] The diuretic response to frusemide is impaired because of the fall in arterial pressure and glomerular filtration rate and the withdrawal of atrial natriuretic peptide[40 44] if atrial pressure falls; but, in contrast with other vasodilators, angiotensin II, aldosterone, and sympathetic nervous activity are reduced so sodium retention is limited and does not persist.

Hypotension increases arginine vasopression and may actually cause an early fall in serum sodium, but long term controlled studies have not suggested any overall change.[34 35] Potassium retention begins as soon as ACE inhibitors are started but is not reflected in a rise in serum potassium for days or even weeks.[44] The potassium is retained in the depleted intracellular compartment[45] but the serum potassium eventually rises as the pre-treatment total body potassium depletion is corrected. Potassium sparing diuretics, which may be needed in the early days or weeks of treatment, can, if continued, lead to dangerous hyperkalaemia. Spironolactone is most likely to give rise to problems for the reasons outlined above.

Prediction of effect

Just as there is a poor relation between clinical state and neuroendocrine activation, so activation of these systems is a poor predictor of response to an ACE inhibitor.[46] A modest correlation has been noted between the initial haemodynamic effects and plasma renin, which is lost during long term follow up. The increase in plasma renin in response to the first dose of an ACE inhibitor may be a guide to long term efficacy.[47]

Conclusion

Although direct acting vasodilators might be expected to improve symptoms and exercise performance in heart failure, they have proved disappointing. Once again theoretical considerations have failed to work out in clinical practice. There is compelling evidence that their use in chronic heart failure leads to further neuroendocrine activation and that it is this which limits their therapeutic efficacy.

ACE inhibitors were introduced as a new class of vasodilator agent and once again medical serendipity seems to be operating. ACE inhibitors are more than mere vasodilator agents. Indeed their vasodilator actions may not even be a necessary part of their therapeutic effect. The reason for their efficacy remains to be established. Perhaps it is because they induce haemodynamic tolerance only infrequently. However, correction of intracellular electrolyte disturbances, changes in renal sodium and water handling, in the constitution of the vessel wall, and effects on cardiovascular sympathetic control may all contribute to the efficacy of these agents.

1 McMichael J. Circulatory failure studied by means of venous catheterisation. *Adv Intern Med* 1947;2 64–101.

2 Wood P. *Disease of the heart and circulation*. London: Eyre and Spottiswoode, 1950.

3 Braunwald E The control of ventricular function in man. *Br Heart J* 1965,27:1-16.

4 Osler W. *The principles and practice of medicine* New York, London D Appleton, 1892.626–7.

5 Savill TD *A system of clinical medicine*. London: Edward Arnold, 1936.

6 Hayward GW. Tetraethyl ammonium bromide in hypertension and hypertensive heart failure. *Lancet* 1948,1:18–20.

7 Johnson JB, Gross JF, Hale E. Effects of sublingual administration of nitroglycerine in pulmonary artery pressure in patients with failure of the left ventricle. *N Engl J Med* 1957,257·1114-7.

8 Majid PA, Sharma B, Taylor SH. Phentolamine for vasodilator treatment of severe heart failure. *Lancet* 1971;ii:719-24.

9 Harris P. Congestive cardiac failure: central role of the arterial blood pressure. *Br Heart J* 1987;58.190-203.

10 Cleland JGF, Dargie HJ. Heart failure, renal function and angiotensin converting enzyme inhibitors. *Kidney Int* 1987;31(suppl 20) S-220-8

11 Richards AM, Cleland JGF, Tonolo G, McIntyre GD, Leckie BJ, Dargie HJ, *et al.* Plasma a natriuretic peptide in cardiac impairment. *BMJ* 1986;293·409-12.

12 Watkins L Jr, Burton JA, Haber E, Cant JR, Smith FW, Barger AC. The renin-angiotensin-aldosterone system in congestive failure in conscious dogs. *J Clin Invest* 1976;57.1606-17.

13 McAlpine HM, Morton JJ, Leckie B, Rumley A, Gillen G, Dargie HJ. Neuroendocrine activation after acute myocardial infarction *Br Heart J* 1988;60·117-24.

14 Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. *Circulation* 1990,82:1730-6

15 Dargie HJ, Cleland JGF, Leckie BJ, Inglis CG, East BW, Ford I. Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure *Circulation* 1987;75(suppl IV):IV-98–107.

16 Kremer D, Lindop G, Brown WC, Morton JJ, Robertson JI. Angiotensin-induced myocardial necrosis and renal failure in the rabbit: distribution of lesions and severity in relation to plasma angiotensin II concentration and arterial pressure. *Cardiovasc Res* 1981;15:43-6.

17 Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J* 1987,57·17-22.

18 Franciosa JA, Weber KT, Levine TB, Kinasewitz GT, Janicki JS, West J, *et al.* Hydralazine in the long-term treatment of chronic heart failure: lack of difference from placebo. *Am Heart J* 1982;104·587-94.

19 Tan LB, Murray RG, Littler WA. Felodipine in patients with chronic heart failure: discrepant haemodynamic and clinical effects. *Br Heart J* 1987;58 122-8.

20 Bayliss J, Norell MS, Canepa-Anson R, Reid C, Poole-Wilson P, Sutton G. Clinical importance of the renin-angiotensin system in chronic heart failure. double blind comparison of captopril and prazosin. *BMJ* 1985;290:1861-5.

21 Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Co-operative Study. *N Engl J Med* 1986;314 1547-52.

22 Leier CV, Huss P, Magorien RD, Unverferth DV. Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for conjestive heart failure. *Circulation* 1983;67 817-22.

23 Aronow WS, Lurie M, Turbow M, Whittaker K, van Camp S, Hughes D. Effect of prazosin vs placebo on chronic left ventricular failure. *Circulation* 1979;59:344-50.

24 Wilson JR, Ferraro N. Circulatory improvement after hydralazine or isosorbide dinitrate administration in patients with heart failure *Am J Med* 1981;71:627-33.

25 Wilson JR, Ferraro N, Wiener DH. Effect of the sympathetic nervous system on limb circulation and metabolism during exercise in patients with heart failure. *Circulation* 1985,72:72-81.

26 Coats AJ, Adamopolous S, Meyer TE, Conway J, Sleight P. Effects of physical training in chronic heart failure. *Lancet* 1990;335 63-6

27 Cleland JGF, Dargie HJ, Robertson I, Robertson JIS, East BW. Total body electrolyte composition in patients with heart failure: a comparison with normal subjects and patients with untreated hypertension. *Br Heart J* 1987;58·230-8.

28 Markham RV, Gilmore A, Pettinger WA, Brater DC, Corbett JR, Firth BG Central and regional hemodynamic effects and neurohumoral consequences of minoxidil in severe conjestive heart failure and comparison to hydralazine and nitroprusside. *Am J Cardiol* 1983;52 774-81.

29 Colucci WS, Williams GH, Braunwald E Clinical, haemodynamic, and neuroendocrine effects of chronic prazosin therapy for congestive heart failure. *Am Heart J* 1981;102.615-21.

30 Fifer MA, Colucci WS, Lorell BH, Jaski BE, Barry WH Inotropic, vascular and neuroendocrine effects of nifedipine in heart failure. comparison with nitroprusside *J Am Coll Cardiol* 1985;5.731-7.

31 Elkayam U, Weber L, Campese VM, Massry SG, Rahimtoola SH Renal haemodynamic effects of vasodilation with nifedipine and hydralazine. *J Am Coll Cardiol* 1984;4 1261-7

32 Rouleau JL, Warnica JW, Burgess JH. Prazosin and congestive heart failure: short and long term therapy *Am J Med* 1981,71·147-52

33 Riegger GA, Haeske W, Kraus C, Kromer EP, Kochsiek K Contribution of the renin angiotensin aldosterone system to development of tolerence and fluid retention in chronic congestive heart failure during prazosin treatment *Am J Cardiol* 1987;59 906-10.

34 Cleland JGF, Dargie HJ, Hodsman GP, Ball SG, Robertson JIS, Morton JJ, *et al* Captopril in heart failure A double blind controlled trial. *Br Heart J* 1984;52 530-5.

35 Cleland JGF, Dargie HJ, Ball SG, Gillen G, Hodsman GP, Morton JJ, *et al.* Effects of enalapril in heart failure. a double blind study of effects on exercise performance, renal function, hormones, and metabolic state *Br Heart J* 1985;54 305-12.

36 The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalopril Survival Study (CONCENSUS) *N Engl J Med* 1987;316·1429-35.

37 Agostoni PG, De Cesare N, Doria E, Polese A, Tamborini G, Guazzi MD. Afterload reduction. a comparison of captopril and nifedipine in dilated cardiomyopathy *Br Heart J* 1986;55.391-9.

38 Mancini DM, Davis L, Wexler JP, Chadwick B, LeJemtel TH. Dependence of enhanced maximal exercise performance on increased peak skeletal muscle perfusion during long-term captopril therapy *J Am Coll Cardiol* 1987;10 845-50.

39 Cleland J, Semple P, Hodsman P, Ball S, Ford I, Dargie H Angiotensin II levels, haemodynamics and sympatho-adrenal function after low-dose captopril in heart failure. *Am J Med* 1984,77:880-6

40 Cleland JGF. Angiotensin converting enzyme inhibitors in congestive heart failure first-line or second-line therapy? *Eur Heart J* 1990;11(suppl D) 53-7.

41 Cleland JGF, Dargie HJ, McAlpine H, Ball SG, Morton JJ, Robertson JIS, *et al.* Severe hypotension after first dose of enalopril in heart failure. *BMJ* 1985,291:1309-12

42 Cleland JGF, Dargie HJ, Morton JJ Effects of enalapril on diurnal variations in neuroendocrine and electrolyte status in heart failure. *Cardiovascular Drugs and Therapy* 1987;1 221.

43 Rouleau JL, Bichet D, Kortas C. Atrial natriuretic peptide in congestive heart failure postural changes and reset with chronic captopril therapy. *Am Heart J* 1988,115:1060-7

44 Cleland JGF, Gillen G, Dargie HJ The effects of frusemide and angiotensin-converting enzyme inhibitors and their combination on cardiac and renal haemodynamics in heart failure. *Eur Heart J* 1988,9:132-41

45 Cleland JGF, Dargie HJ, East BW, Robertson I, Hodsman GP, Ball SG, *et al.* Total body and serum electrolyte composition in heart failure: the effects of captopril. *Eur Heart J* 1985;6 681-8

46 Packer M, Medina N, Yushak M, Lee WH Usefulness of plasma renin activity in predicting haemodynamic and clinical responses and survival during long term converting enzyme inhibition in severe chronic heart failure. Experience in 100 consecutive patients *Br Heart J* 1985;54 298-304.

47 Packer M, Medina N, Yushak M Efficacy of captopril in low-renin congestive heart failure: importance of sustained reactive hyperreninemia in distinguishing responders from non-responders. *Am J Cardiol* 1984;315 847-53.

Br Heart J 1991;66:268–76

ORIGINAL ARTICLES

Relation between cyclic variation in echo amplitude and segmental contraction in normal and abnormal hearts

David A Lythall, Ron B Logan-Sinclair, Charles J D Ilsley, Sudhir S Kushwaha, Magdi H Yacoub, Derek G Gibson

Departments of Cardiology and Cardiac Surgery, Harefield Hospital, Middlesex
D A Lythall
C J D Ilsley
S S Kushwaha
M H Yacoub

Department of Biomedical Engineering, Royal Brompton National Heart and Lung Hospital, London
R B Logan-Sinclair

Department of Cardiology, Royal Brompton National Heart and Lung Hospital, London
D G Gibson

Correspondence to
Dr David A Lythall,
Flat 1,
3 Gloucester Crescent,
London NW1 7DS

Accepted for publication
16 April 1991

Abstract

Objective—To study the relation between cardiac systolic activity and cardiac cycle dependent variation in the ultrasound signal arising from within the myocardium.

Design—Regional echo amplitude was used as a measure of the myocardial ultrasound signal. Relative echo amplitude values were assigned by standardising echo gain using the posterior parietal pericardium as an in-vivo calibration. M mode measurements of the left ventricle were used to assess cardiac systolic activity. Subjects were studied prospectively. Analysis of echo amplitude was performed by investigators who were blinded to the results of the M mode analysis. The influence of impaired left ventricular performance and abnormal wall motion were assessed.

Patients—11 cardiomyopathy patients with impaired ventricular function, eight patients with severe pulmonary hypertension and reversed septal motion, and 19 healthy controls.

Setting—All subject studies were performed at Harefield Hospital. Echo amplitude analysis was performed at the Royal Brompton Hospital.

Main outcome measures—Cyclic variation in echo amplitude was determined as the change in echo amplitude from end diastole to end systole. Additionally, an index of cyclic variation defined as the ratio of the cyclic change in echo amplitude to end diastolic echo amplitude was measured. Both cyclic variation and the cyclic variation index were analysed to see whether they correlated with left ventricular dimensions, fractional shortening, and systolic wall thickening.

Results—Stepwise regression analysis showed systolic wall thickening to be the most significant independent variable that correlated with the cyclic variation index for both the septum and posterior wall ($r = 0{\cdot}68$, $p = 0{\cdot}0001$, septum; $r = 0{\cdot}69$, $p = 0{\cdot}0001$, posterior wall). The slopes and intercepts for both regression equations were similar ($y = 0{\cdot}005x + 0{\cdot}006$, septum; $y = 0{\cdot}006x + 0$, posterior wall). Subgroup analysis showed that the healthy controls, patients with cardiomyopathy, and patients with pulmonary hypertension had similar slopes and intercepts for their individual regression equations.

Conclusions—These data support the hypothesis of a quantitative relation between the extent of cyclic variation of echo amplitude and the degree of segmental myocardial shortening, as measured by systolic wall thickening, which is not significantly influenced by location within the myocardium, left ventricular performance, or wall motion. They provide further evidence of the usefulness of quantitative analysis of myocardial echo amplitude in the study of regional myocardial function in both normal and injured myocardium.

Ultrasonic tissue characterisation provides a powerful non-invasive tool for examining myocardial structure and function in both normal and disease states.[1–10] Previous workers have shown a cardiac cycle dependent variation in ultrasound signals from within the myocardium in humans and animals.[9 11–13] Peak values occurred at end diastole and minimum values at end systole. It has been suggested that these cyclic changes are related to contractile events within the myocardium.[14] The extent of the relation between contractile events and cyclic variation in the ultrasound signal, however, is still unclear, particularly in human hearts both normal and diseased.

During cardiac contraction several physiological events occur within the myocardium including wall thickening, motion of the wall, and an increase in myocardial tension. Their effects on the myocardial ultrasound signal cannot easily be distinguished from each other in animal preparations—for example an increase in cardiac contractility may increase all three of these measurements, obscuring the individual contribution of each. For these reasons we have studied three different subject groups to study the effect of these physiological events on echo amplitude in humans. The three groups studied consisted of healthy volunteers in whom wall motion, thickening,

Table 1 Clinical details for normal subjects

No	Age	Sex	Heart rate (beats/min)
1	25	M	72
2	28	M	68
3	35	M	84
4	21	M	60
5	29	M	68
6	27	M	64
7	25	M	60
8	24	M	84
9	30	M	50
10	30	M	78
11	26	M	64
12	29	M	48
13	34	M	52
14	32	M	78
15	26	M	52
16	24	M	63
17	27	M	52
18	27	M	64
19	26	M	68

and tension were normal; patients with cardiomyopathy in whom wall thickening and motion were decreased throughout the cycle (that is, not hypertrophic cardiomyopathy), and patients with pulmonary hypertension in whom wall thickening was normal but wall motion was abnormal. We used regional echo amplitude (echo amplitude) as a measure of the ultrasound signal arising from within the myocardium.[2]

Patients and methods

We studied 19 healthy male volunteers (age 21–35 years, mean 27·6 years), 11 patients with cardiomyopathy (four female, age 21–59 years, mean 41·9 years) referred for cardiac transplant assessment, and eight patients with severe pulmonary hypertension (seven female, age 26–58 years, mean 32·6 years) referred for heart-lung transplant assessment. Table 1 shows the clinical details of the controls and table 2 of patients with cardiomyopathy or pulmonary hypertension. Two patients with cardiomyopathy were in atrial fibrillation, all other patients were in sinus rhythm. Subjects gave informed consent and the study was approved by the hospital ethics committee.

CROSS SECTIONAL AND M MODE ECHOCARDIOGRAPHY

M mode and cross sectional echocardiography were performed on a Toshiba SSH-65A echocardiograph with patients in the left lateral position. A 2·5 MHz transducer was used. Long axis parasternal M mode echograms of the left ventricle were made at the level of the mitral valve leaflet tips and were recorded on a strip chart recorder at a paper speed of 100 cm/s. Measurements were made from leading edge to leading edge and all values were the mean of five cardiac cycles. End diastolic values were measured at the onset of the Q wave of the electrocardiogram and end systolic values at maximum posterior displacement of the septum except in those patients with reversed septal motion, in whom we used maximum anterior displacement of the posterior wall to define end systole. Posterior wall and septal thickening was defined as end systolic thickness minus end diastolic thickness in millimetres (mm) and fractional shortening of the posterior wall and septum was defined as the respective change in wall thickness expressed as a percentage (%) of the diastolic dimension.

ECHO AMPLITUDE STUDIES

Echo amplitude studies were recorded with a 3·5 MHz Advanced Technology Laboratories (ATL) (720A/8736 series) mechanical sector scanner and an ATL (860-1 series) echocardiograph system with 45 dB logarithmic grey scale compression. Self correcting circuits were inactivated to avoid further differentiation of the original echo signal. Images were simultaneously displayed in grey scale and in colour by a Brompton encoder as they were recorded. Gain settings were standardised at the time the recordings were made: the master gain was increased until the parietal pericardium posterior to the left ventricle was just displayed at the highest level on the encoder (white). The depth compensation was then set to a linear ramp across the image at a rate of approximately 2 dB/cm. Gain settings were not altered thereafter. Parasternal long axis views in the left lateral position were recorded. Images were stored on U-matic 3/4 inch video tape by a Sony VO 5800PS recorder. We used a Tandon PCA desk top computer for analysis. We selected stop frame end diastolic and end systolic images for analysis using a tape recorder with digital frame advance (Sony VO 5800PS). These frames were transferred from tape to a 512 × 256 × 6 bit frame store. Images were processed by an adaptive filtering process to reduce speckle because this decreased echo amplitude variance and allowed smaller sample sizes to be used.[15,16] Areas of interest were defined in the basal ventricular septum and posterior wall corresponding to the level of the M mode scan and measurements of 256 individual picture elements (pixels) were made from each area. Four separate measurements each of 64 pixels were made and averaged rather than one individual

Table 2 Clinical details of patients with cardiomyopathy or pulmonary hypertension

No	Age	Sex	Heart rate (beats/min)	Aetiology
Cardiomyopathy.				
1	21	M	94	DCM
2	54	M	71	DCM
3	23	F	135	DCM
4	24	F	67	RCM*
5	40	M	69	Sarcoid
6	51	M	105	Sarcoid*†
7	53	M	80	Sarcoid
8	59	M	60	DCM
9	53	F	122	DCM
10	53	M	105	DCM†
11	30	F	100	DCM*
Pulmonary hypertension:				
12	27	F	71	PPH
13	29	F	120	PPH
14	26	F	60	EISEN
15	28	M	77	PPH
16	33	F	75	PPH
17	32	F	87	EISEN
18	58	F	83	PH/TE
19	28	F	91	EISEN

DCM, dilated cardiomyopathy, EISEN, Eisenmenger's syndrome; PH/TE, pulmonary hypertension secondary to thromboembolic disease, PPH, primary pulmonary hypertension, RCM, restrictive cardiomyopathy

*Abnormal septal motion, †atrial fibrillation.

Table 3 *M mode measurements (mm) in healthy controls*

No	*LVED*	*LVES*	*FS%*	*PWd*	*PWs*	*PWFS%*	*Sd*	*Ss*	*SFS%*	*LA*
1	45	33	38	10 0	13·6	36	9 1	10·9	20	28
2	44	27	38	7·4	12·1	64	8 4	12 1	44	34
3	51	34	34	8 1	13 8	69	6 9	13·1	91	38
4	46	30	35	10·0	15·0	50	13 3	18 8	42	30
5	48	31	35	8·2	12·4	50	10 0	14 1	41	32
6	50	31	38	8 8	13 1	50	7 5	11 3	50	34
7	49	30	37	8 1	16·0	97	10 0	12 5	25	38
8	51	31	39	8 8	14 1	60	7 1	12 9	82	37
9	50	31	38	9 4	15 0	60	10 0	15 0	50	38
10	54	33	37	7 5	13 8	83	8 8	13 8	57	38
11	53	34	36	10 0	15 0	50	8 8	13 8	57	30
12	48	30	37	12 5	17 5	40	12 5	17 5	40	41
13	45	29	36	10 1	15 4	52	8 7	15 1	74	33
14	46	33	29	7 5	13 1	73	9 3	12 5	34	44
15	48	31	35	10·7	15 4	44	9 3	12 4	33	39
16	39	23	40	7 1	10 3	45	7 6	10 9	43	20
17	47	29	39	9 9	14 9	51	10 0	13 8	38	30
18	49	31	37	7 3	12·4	69	7 2	12 0	63	32
19	52	38	28	8·3	14·6	77	10·6	17 5	65	41
Mean (SD)	48 (3 4)	31 (2·9)	36 (3·2)	8 9 (1 4)	14 1 (1 6)	59 (15·9)	9 2 (1 7)	13 7 (2 3)	50 (18 7)	35 (5 6)

FS%, percentage fractional shortening of left ventricle, LA, left atrial dimension; LVED, left ventricular end diastolic dimension; LVES, left ventricular end systolic dimension, PWd, Posterior wall end diastolic thickness; PWFS%, percentage posterior wall systolic thickening; PWs, posterior wall end systolic thickness; Sd, septal end diastolic thickness, SFS%, percentage septal systolic thickening, Ss, septal end systolic thickness.

measurement of 256 pixels because this allowed the pixel matrix to be placed within the mid-myocardium and thus avoided including specular echoes from the endocardium or epicardium. A maximum pixel intensity for each image was derived by measuring the maximum colour intensity of the superimposed colour scale. This corresponded to a value of 45 dB thus allowing echo amplitude values to be assigned. A value of 0 dB would therefore correspond to a level −45 dB below the parietal pericardial echo amplitude. Individual pixel amplitudes were displayed as a histogram and a separate digital readout displayed mean, median, and standard deviation values for each region measured. In addition to values of echo amplitude at end diastole and end systole, an index of the change in echo amplitude during the cardiac cycle (cyclic variation index) was calculated as the ratio of end diastolic echo amplitude minus end systolic echo amplitude to end diastolic echo amplitude.

STATISTICAL ANALYSIS

All values are expressed as mean (SD). We used stepwise multivariate and univariate linear regression analysis to analyse the relation between echo amplitude and M mode measurements, age, and heart rate. Intergroup comparisons were made by two tailed *t* testing. A probability level of $p < 0.05$ was regarded as significant.

Results

Images suitable for analysis were available in all but one control in whom an adequate end systolic image of the septum could not be obtained and in two patients with severe pulmonary hypertension in whom adequate views of the septum could not be obtained in either systole or diastole. In one patient with pulmonary hypertension left atrial dimensions could not be measured reliably. Table 3 shows the M mode values for individual subjects.

Table 4 *M mode measurements (mm) in patients with cardiomyopathy or pulmonary hypertension*

No	*LVED*	*LVES*	*FS%*	*PWd*	*PWs*	*PWFS%*	*Sd*	*Ss*	*SFS%*	*LA*
Cardiomyopathy:										
1	70	64	8	7 2	8 3	15	7 2	7·8	8	46
2	80	73	9	6 6	7 9	19	6 6	7 9	19	76
3	55	51	7	11 4	12 9	13	10 0	11 4	14	36
4	38	29	24	10 0	13 0	30	10 5	13 0	24	46
5	56	46	18	9 0	14 5	61	14 5	18 0	24	45
6	29	22	24	7 0	11 0	57	9 0	12·0	33	41
7	102	94	8	5 5	6 0	9	5 0	7 0	30	32
8	64	44	31	8 5	14 0	65	8 5	13 0	53	42
9	59	55	7	5 5	6 0	9	6 0	6 5	8	37
10	82	67	18	11 0	13 0	18	11 0	12·0	9	59
11	56	53	5	9 5	10 5	11	7 0	7 3	4	39
Mean (SD)	63 (20 4)	54 (20 1)	14 (8 9)	8 3 (2·1)	10 6 (3 1)	28 (22 2)	8 7 (2·7)	10 5 (3 6)	21 (14 5)	45 (12 4)
Pulmonary hypertension.										
12	28	10	29	8 0	11 0	38	9 0	15 0	67	19
13	38	11	71	7 0	10 0	42	5 5	7 5	36	36
14	55	27	51	10 0	14 5	45	10 5	15 0	43	*
15	41	32	22	8 5	13 0	53	10 5	14 0	33	30
16	27	13	59	9 0	12 0	33	8·5	12·0	41	28
17	32	23	28	6·0	8 5	42	6 0	7 0	13	31
18	25	12	52	7 0	10 0	43	7 3	9 0	23	26
19	35	26	26	8 0	11·0	38	7 0	8 5	21	29
Mean (SD)	35 (9 8)	19 (8·7)	42 (18 3)	7 9 (1·3)	11 3 (1 9)	42 (5·9)	8 0 (1 9)	11 0 (3 4)	35 (16·6)	28 (5 2)

*Could not be measured
See table 3 for all other abbreviations.

VENTRICULAR SEPTAL MOTION

All the patients with pulmonary hypertension had reversed ventricular septal motion with considerable bowing of the interventricular septum into the left ventricle. Three patients in the cardiomyopathy group also had abnormal septal motion: two patients because of left bundle branch block and one associated with severe pulmonary hypertension. All the other subjects had normal septal motion.

LEFT VENTRICULAR AND LEFT ATRIAL DIMENSIONS (TABLES 3 AND 4)

Left ventricular end diastolic dimension and end systolic dimension were greater ($p < 0{\cdot}005$) and percentage fractional shortening was less ($p < 0{\cdot}001$) in the patients with cardiomyopathy than in the healthy controls, reflecting the poor left ventricular systolic function of the cardiomyopathy patients. Left ventricular dimensions in the patients with pulmonary hypertension were significantly lower than for the healthy controls ($p < 0{\cdot}001$) although fractional shortening was maintained reflecting the apparent distortion of left ventricular shape and the smaller body mass of these patients (seven of the eight patients were female). The right ventricular cavity was considerably enlarged and the right ventricular free wall appeared to be thickened in the patients with pulmonary hypertension.

WALL THICKENING

Tables 3 and 4 show the values for posterior wall and septal thickness. The mean end systolic wall thickness of the posterior wall and septum was significantly lower in the cardiomyopathy patients than in the healthy controls ($p < 0{\cdot}01$), again reflecting the grossly impaired contractile function of these patients' hearts. Similarly, percentage systolic thickening of both the posterior wall and the septum was significantly lower ($p < 0{\cdot}0001$). Systolic wall thickening was preserved in the patients with pulmonary hypertension and reversed septal motion. For both the controls and the patients with pulmonary hypertension, wall thickening was within the normal range reported by others.[17]

REGIONAL ECHO AMPLITUDE (TABLES 5 AND 6)

The mean echo amplitude in the septum of the healthy controls was significantly greater at end diastole than end systole ($p = 0{\cdot}0001$). A similar variation during the cardiac cycle was seen in the posterior wall ($p = 0{\cdot}0001$). Figure 1 shows representative end diastolic and end systolic echo amplitude images from a healthy volunteer. In the patients with pulmonary hypertension we saw variation in echo amplitude of a similar magnitude, greatest at end diastole and least at end systole, in the septum ($p < 0{\cdot}05$) and posterior wall ($p < 0{\cdot}001$). In contrast, the variation in echo amplitude during the cardiac cycle was considerably blunted in the poorly contractile left ventricles of the patients with cardiomyopathy. In three patients with cardiomyopathy with greatly reduced posterior wall thickening and in one with very reduced septal thickening (cardiomyopathy patients 3, 7, 9 and 11 respectively) echo amplitude at end systole was slightly higher than at end diastole. The index of echo amplitude cyclic variation was less in the patients with cardiomyopathy than in the healthy controls (septum, $p = 0{\cdot}09$; posterior wall, $p < 0{\cdot}001$) and in the patients with the pulmonary hypertension (septum, $p = 0{\cdot}01$; posterior wall, $p = 0{\cdot}001$).

ECHO AMPLITUDE CYCLIC VARIATION VERSUS SYSTOLIC WALL THICKENING

Stepwise linear regression analysis showed that systolic wall thickening was the most important independent determinant of echo amplitude cyclic variation, measured as the cyclic variation index (table 7). The slopes and intercepts of the regression relation for both the septum ($y = 0{\cdot}005x + 0{\cdot}06$) and posterior wall ($y = 0{\cdot}006x + 0{\cdot}004$) were similar (fig 2), suggesting that at least in the base of the left ventricle the relation between cyclic variation in echo

Table 5 Regional echo amplitude values in healthy controls

No	*SEAd (dB)*	*SEAs (dB)*	*SCVI*	*PWEAd (dB)*	*PWEAs (dB)*	*PWCVI*
1	2·79	2·58	0·07	3·63	3·57	0·02
2	2·83	2·44	0·14	4·03	2·16	0·46
3	4·03	2·10	0·48	4·43	2·98	0·33
4	2·48	2·15	0·13	5·70	3·16	0·45
5	5·15	4·18	0·19	5·35	4·40	0·18
6	3·43	2·62	0·24	3·53	2·25	0·36
7	3·01	2·87	0·05	5·09	2·74	0·46
8	2·83	2·13	0·25	3·12	2·44	0·22
9	3·13	1·77	0·43	2·25	1·89	0·16
10	3·90	2·91	0·25	4·09	2·58	0·37
11	1·77	*	*	4·32	3·20	0·26
12	2·45	1·90	0·23	2·96	2·61	0·12
13	4·65	2·76	0·41	3·45	1·96	0·43
14	3·65	2·81	0·23	4·10	2·44	0·40
15	3·56	2·66	0·25	4·12	2·41	0·41
16	4·54	3·29	0·28	3·05	2·59	0·15
17	2·98	2·50	0·16	4·18	2·19	0·48
18	3·43	2·47	0·28	3·81	2·37	0·38
19	4·02	1·83	0·54	4·06	2·05	0·50
Mean (SD)	3·40 (0·85)	2·55 (0·58)	0·26 (0·14)	3·96 (0·84)	2·63 (0·62)	0·32 (0·14)

PWEAd, posterior wall end diastolic echo amplitude (dB); PWEAs, posterior wall end systolic echo amplitude (dB); PWCVI, posterior wall cyclic variation index ((PWEAd − PWEAs) − PWEAd); SEAd, septal end diastolic echo amplitude (dB); SEAs, septal end systolic echo amplitude (dB); SCVA, septal cyclic variation index ((SEAd − SEAs) − SEAd).
*Could not be measured.

Table 6 Regional echo amplitude in patients with cardiomyopathy or pulmonary hypertension

No	*SEAd (dB)*	*SEAs (dB)*	*SCVI*	*PWEAd (dB)*	*PWEAs (dB)*	*PWCVI*
Cardiomyopathy:						
1	7·48	5·73	0·23	14·70	12·38	0·16
2	7·88	7·71	0·02	8·68	7·86	0·09
3	8·31	7·95	0·04	9·83	10·07	−0·02
4	6·56	5·23	0·20	7·01	4·77	0·32
5	8·05	6·42	0·20	7·29	6·89	0·06
6	6·82	3·64	0·47	7·24	5·43	0·25
7	7·24	5·90	0·19	7·18	7·76	−0·08
8	5·23	3·68	0·30	8·52	5·82	0·32
9	8·97	7·94	0·12	12·28	13·73	−0·12
10	7·86	7·32	0·07	8·38	7·85	0·06
11	10·74	11·19	−0·04	8·37	7·98	0·05
Mean (SD)	7·74 (1·41)	6·61 (2·17)	0·16 (0·14)	9·04 (2·41)	8·32 (2·81)	0·10 (0·15)
Pulmonary hypertension:						
12	8·82	3·97	0·55	6·05	4·20	0·31
13	4·73	2·63	0·44	3·50	2·33	0·33
14	2·66	1·76	0·34	5·53	3·05	0·45
15	3·61	2·50	0·31	4·28	2·00	0·53
16	4·52	2·47	0·45	4·35	3·26	0·25
17	2·18	1·87	0·14	4·03	3·18	0·21
18	*	*	*	8·99	5·86	0·35
19	*	*	*	9·84	7·26	0·26
Mean (SD)	4·42 (2·38)	2·55 (0·79)	0·37 (0·14)	5·82 (2·37)	3·89 (1·81)	0·34 (0·11)

See footnote to table 5 for abbreviations.

amplitude and systolic wall thickening is independent of position within the ventricle and mainly reflects the degree of wall thickening. Analysis of the three groups individually confirmed a similar relation within each group. The slopes and intercepts of the regression relation were similar in the healthy controls and patients with cardiomyopathy but there was some variation in these values in the patients with pulmonary hypertension (figs 3 and 4). However, there was a large overlap in the 95% confidence intervals for the slopes between the three groups. The correlation between the absolute change in echo amplitude (as distinct from cyclic variation index) and systolic wall thickening was less (r = 0·42, p = 0·01, septum all subjects; r = 0·47, p = 0·003, posterior wall all subjects), suggesting that the incorporation of a factor, in this case end diastolic echo amplitude, which reflects the overall background level of echo amplitude within the myocardium, is important.

ECHO AMPLITUDE CYCLIC VARIATION VERSUS CAVITY DIMENSION, WALL THICKNESS, HEART RATE, AND AGE

Systolic but not diastolic wall thickness was significantly correlated with the cyclic variation index for both the septum (r = 0·36, p = 0·02) and posterior wall (r = 0·50, p = 0·002) in all subjects. The left ventricular end diastolic dimension was significantly negatively correlated with the cyclic variation index, both for the septum (r = −0·42, p = 0·02) and posterior wall (r = −0·45, p = 0·005) as was left ventricular end systolic dimension (septum, r = −0·51; p = 0·002: posterior wall, r = −0·58; p = 0·0001). Left ventricular fractional shortening was also significantly correlated with cyclic variation index (septum, r = 0·48; p = 0·004: posterior wall, r = 0·53; p = 0·001). These results are consistent with the major influence of systolic wall thickening on overall left ventricular performance. Heart rate and age were negatively correlated with the cyclic variation index in the posterior wall (heart rate, r = −0·48; p = 0·003: age, r = −0·35; p = 0·03) but no similar correlation was seen for the septum. The negative correlation with heart rate seemed to reflect the strong association between poor left ventricular function and the higher heart rates observed clinically.

REPRODUCIBILITY OF ECHO AMPLITUDE MEASUREMENTS

To measure the reproducibility of this technique, 30 end diastolic (3·28–7·84 dB) and 30 end systolic (2·96–4·88 dB) measurements were analysed on two separate occasions by the same observer (DL). The mean difference between repeated end diastolic measurements was −0·05 (SD 0·58) dB. For end systolic measurements the mean difference was −0·02 (SD 0·60) dB.

Discussion

We found a quantitative relation between cyclic variation in echo amplitude and segmental contractile events, as reflected by systolic wall thickening, within the myocardium of human subjects. This relation seemed to be valid over a wide range of both physiological and pathological degrees of left ventricular performance, even in the presence of distorted wall motion as illustrated by those patients with severe pulmonary hypertension and reversed septal motion. It seemed to be relatively independent of alterations in wall tension—in that myocardium with presumed increased levels of wall tension (dilated cardiomyopathies) behaved similarly to myocardium with normal values (controls) and probably also to myocardium with decreased values (left ventricular posterior wall in reversed septal motion). Similarly, local geometric factors such as diastolic wall thickness had little influence. Global left ventricular characteristics such as left ventricular dimension and fractional shor-

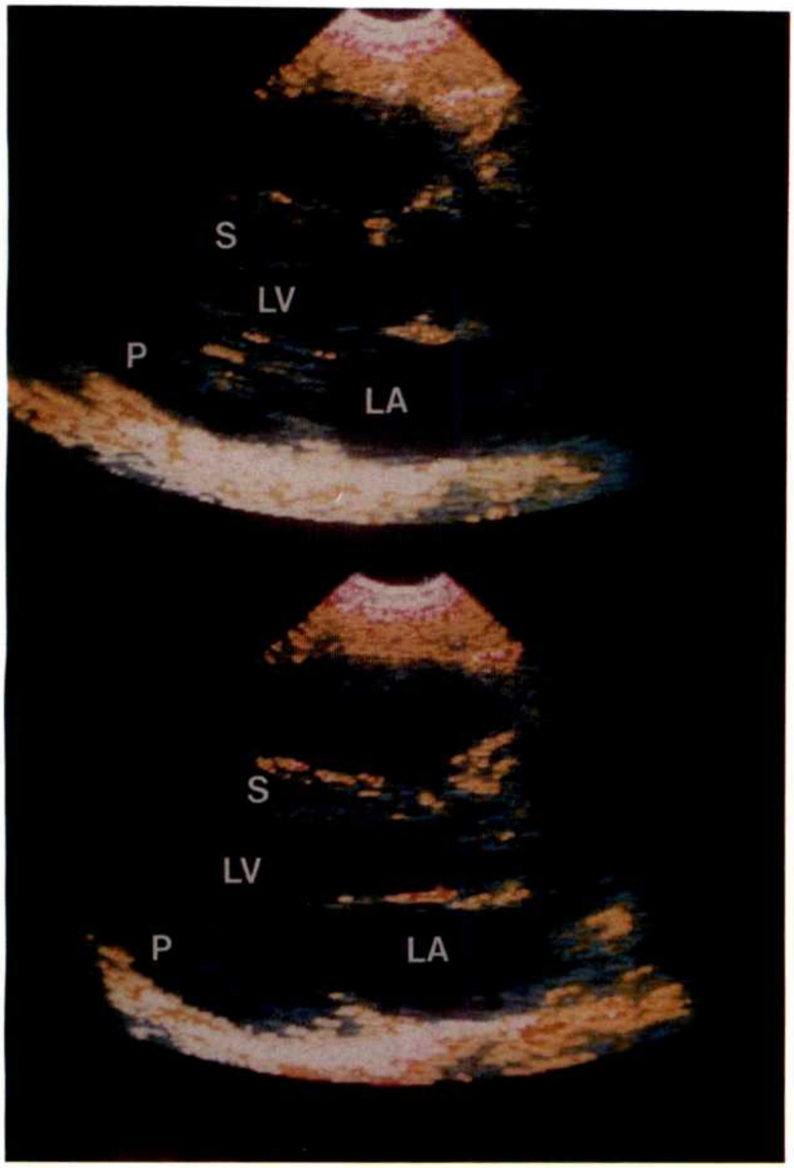


Figure 1 Representative colour-encoded images from a healthy control. (Top) End systolic frame and (bottom) preceding end diastolic frame. Dark blue represents the lowest levels of echo amplitude, which progresses through green, yellow, red, and purple to white, the highest level of echo amplitude. The myocardium of the posterior wall and interventricular septum at end diastole is predominantly green-blue. The amplitude intensity of echoes from the same areas of myocardium at end systole (predominantly dark blue) was less than at end diastole. The higher amplitude echoes seen anterior to (above) the posterior wall in the end systolic image are related to the mitral valve apparatus. S, interventricular septum; LA, left atrium; LV, left ventricular cavity; P, posterior wall.

tening related to cyclic variation in echo amplitude only in so far as they substantially reflected the influence of systolic wall thickening on overall left ventricular performance.

PREVIOUS HUMAN AND ANIMAL STUDIES

There is considerable evidence for a causal relation between cyclic variation and cardiac systolic activity. In animal models it has been shown that interventions that depress myocardial function, such as ischaemia, cause a blunting of cyclic variation in the myocardial ultrasound signal, in this case integrated backscatter.[13] Wickline *et al* used paired pacing and propranolol to modify myocardial contractility in open chested dogs and they showed that the maximum negative rate of change of integrated backscatter ($-dIB/dt_{max}$) seemed to change in parallel with global contractile function measured by the maximum rate of change of left ventricular pressure (dP/dt_{max}).[18] However, they were unable to correlate the extent of cyclic variation of integrated backscatter with changes in left ventricular dP/dt_{max}. They did show a regional variation within the left ventricle, the amplitude of cyclic variation being greater in the apical than the basal regions of the ventricle and they suggested that cyclic variation in integrated backscatter may in part be dependent on absolute sarcomere shortening which may be greater in more apical regions of the ventricle. Glueck *et al* also showed a progressive increase in cyclic variation from ventricular base to apex which they suggested paralleled a similar gradation in contractile function.[19] In later experiments Wickline *et al*, again in open chested dogs, showed a significant correlation between another measure of cyclic variation (phase weighted amplitude of cyclic variation) and systolic wall thickening before and during coronary occlusion, and after reperfusion.[20] Below 20% systolic thickening this relation was markedly non-linear with large decrements in phase weighted amplitude occurring with small decreases in systolic thickening. Non-linearity at non-physiological levels of systolic thickening may reflect irreversible or slowly reversible structural or biochemical alterations within the myocardium, since it has previously been shown that the collagen matrix is damaged after even brief periods of ischaemia.[21] These findings are similar to our observations at the very low levels of wall thickening seen in the cardiomyopathy study group, perhaps reflecting the irreversible changes in myocardial structure that occur in end-stage cardiomyopathy. Sagar *et al* studied the effect of heart rate, preload, and inotropic state on cyclic variation and also found a relation with grouped data between cyclic variation and segmental shortening

Table 7 Univariate regression analysis of echo amplitude cyclic variation index compared with percentage systolic thickening

	n	*r*	*r*^{2}	*SE*	*p*	*Intercept*	*Slope*	*SE slope*
Septum:								
All subjects	35	0·68	0·46	0·114	0·0001	0·06	0·005	0·001
Controls	18	0·73	0·53	0·096	0·0006	0·00	0·005	0·001
Cardiomyopathy	11	0·67	0·45	0·113	0·025	0·03	0·007	0·002
PHT	6	0·90	0·81	0·07	0·015	0·09	0·007	0·002
Posterior wall:								
All subjects	38	0·69	0·47	0·126	0·0001	0·00	0·006	0·001
Controls	19	0·54	0·29	0·124	0·018	0·04	0·005	0·001
Cardiomyopathy	11	0·65	0·42	0·120	0·03	−0·02	0·004	0·002
PHT	8	0·83	0·69	0·065	0·01	−0·29	0·015	0·004

n, number; p, probability; PHT, pulmonary hypertension; r, correlation coefficient; SE, standard error.

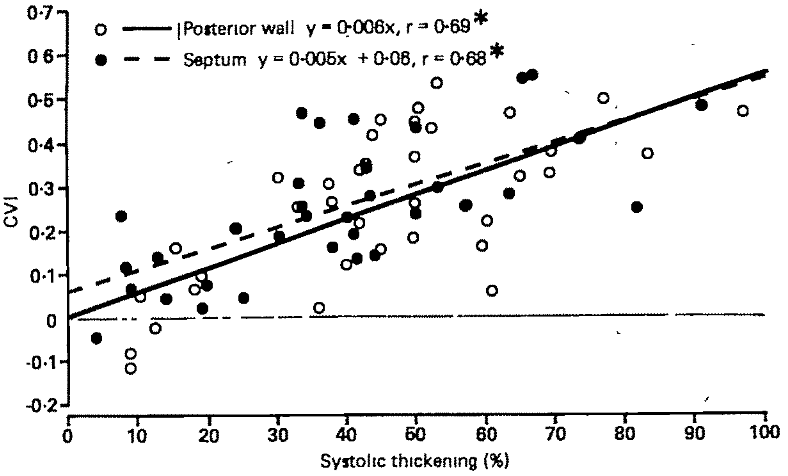


*Figure 2 Cyclic variation index plotted against percentage systolic wall thickening for both the septum and posterior wall for all subjects. The slopes and intercepts for both relations are similar, suggesting that this relation is relatively independent of position within the ventricular myocardium. Cyclic variation index (CVI) = (end diastolic EA – end systolic EA) – end diastolic EA. *p = 0·0001.*

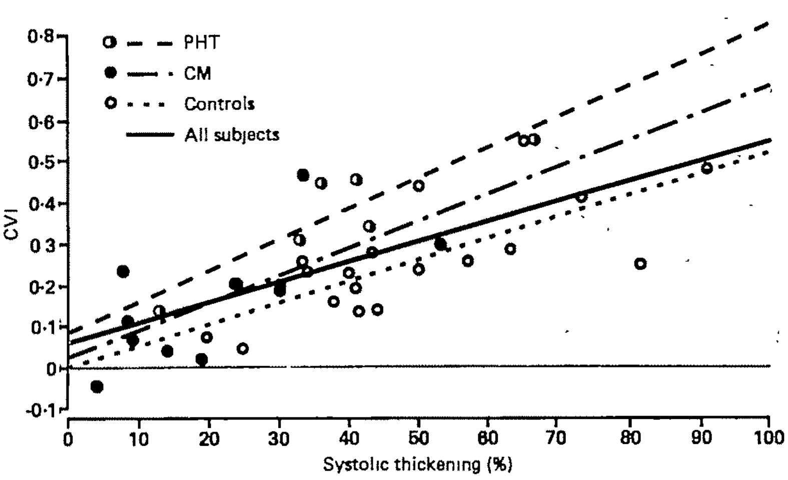


Figure 3 Cyclic variation index plotted against percentage systolic wall thickening for the septum for all three groups. The slopes and intercepts for the series of regressions are similar, suggesting that the relation is independent of left ventricular performance and is not altered in the presence of abnormal wall motion. CM, cardiomyopathy; PHT, pulmonary hypertension. See legend to figure 2 for other abbreviations.

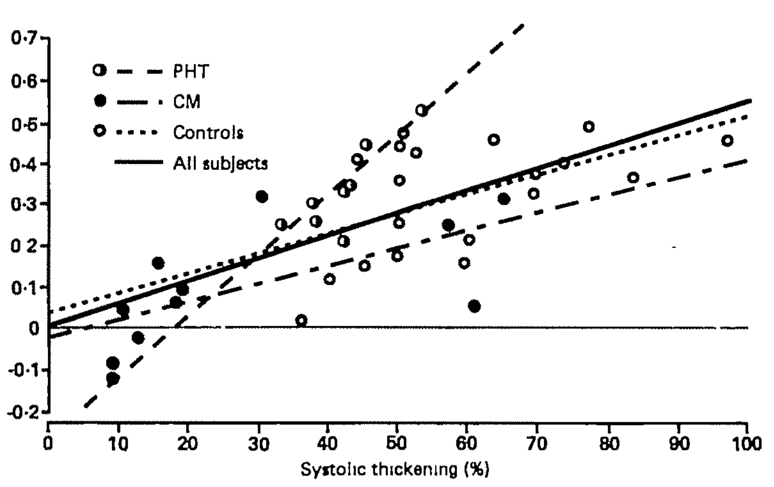


Figure 4 Cyclic variation index plotted against percentage systolic wall thickening for the posterior wall for all three groups. Slopes and intercepts for the series of regressions for controls and patients with cardiomyopathy are similar suggesting that the relation is independent of left ventricular performance. There is some variance with the patients with pulmonary hypertension; however, there is overlap between the 95% confidence intervals for the slopes of all three regression lines. CM, cardiomyopathy; PHT, pulmonary hypertension. See legend to figure 2 for other abbreviations.

directly measured by sonomicrometry and with left ventricular dP/dt_{max}.[22] However, they did not directly correlate segmental shortening with cyclic variation.

Human studies have also suggested a relation between cyclic variation and cardiac systolic activity. Olshansky *et al* analysed regional echo amplitude, using the mean grey level, from cross sectional echocardiograms in 16 healthy controls and confirmed a cyclic variation in echo amplitude.[12] In six subjects digitised stop frame photographs were analysed and in the remaining 10 data were acquired directly from the digital scan converter. They showed an average fall of 17% in echo amplitude (equivalent to a cyclic variation index of 0·17) in the left ventricular posterior wall from end diastole to end systole. This compares with an average cyclic variation index in healthy controls in this study of 0·32 (0·14). We believe this difference reflects the lesser pre-processing of our equipment. Vered *et al*[9] using integrated backscatter measurements also showed cyclic variation in normal human myocardium.[9] They also saw considerably diminished cyclic variation in five patients with dilated cardiomyopathy. Similarly, a study of integrated backscatter in patients at the time of coronary angioplasty showed a blunting of cyclic variation associated with wall motion abnormalities during balloon inflation with a return to baseline after balloon deflation.[23] More recently Milunski and colleagues showed a recovery in cyclic variation, measured using integrated backscatter, in infarcted and peri-infarcted regions after coronary reperfusion associated with thrombolysis.[24] Milunski *et al* have also reported the preservation of cyclic variation in patients with reversed septal motion[25] similar to our findings in patients with pulmonary hypertension. These human studies together with the previous animal experiments indicate a correlation between cyclic variation in the myocardial ultrasound signal and myocardial systolic activity.

The exact basis of this association is as yet unclear. Because systolic thickening is directly related to myocyte shortening, since the shortening myocardial segment must thicken for its volume to remain constant, it is likely that the mechanism that produces cyclic variation in echo amplitude is substantially related to myocyte shortening. It has been suggested that as myocytes contract the acoustic properties of the contractile and elastic elements may alter in disparate directions thus changing the acoustic mismatch and causing a fall in the reflected ultrasound signal.[14] The cyclic variation in the ultrasound signal could thus be modified to parallel contractile events in timing as well as in magnitude. During myocardial contraction myocardial fibre orientation changes[26] and this is also likely to influence the ultrasound signal. The relative uniformity of echo amplitude cyclic variation seen in this study at the base of the heart, in both the septum and posterior wall, as evidenced by the similar slopes and intercepts of the cyclic variation index versus systolic thickening relation, may reflect the similar arrangement of circumferential and circumstances, tissue characterisation may provide more useful information on tissue viability and function.

In conclusion, this study provides evidence that cyclic variation in echo amplitude reflects segmental myocardial shortening in normal and abnormal hearts and this can be measured by analysis of grey scale images from studies acquired in real time.

DAL is a Junior Research Fellow of the British Heart Foundation.

1 Mimbs JW, O'Donnell M, Miller JG, Sobel BE. Changes in ultrasonic attenuation indicative of early myocardial ischemic injury *Am J Physiol* 1979;236(2):H340–4.

2 Logan-Sinclair R, Wong CM, Gibson DG Clinical application of amplitude processing of echocardiographic images *Br Heart J* 1981,45 621–7

3 Parisi AF, Nieminen M, O'Boyle JE, *et al* Enhanced detection of the evolution of tissue changes after acute myocardial infarction using color-encoded two-dimensional echocardiography. *Circulation* 1982,66:764–70.

4 Davies J, Gibson DG, Foale R, *et al*. Echocardiographic features of eosinophilic endomyocardial disease *Br Heart J* 1982;48 434–40

5 Shaw TRD, Logan-Sinclair RB, Surin C, *et al* Relation between regional echo intensity and myocardial connective tissue in chronic left ventricular disease. *Br Heart J* 1984;51 46–53

6 Shapiro LM, Moore RB, Logan-Sinclair RB, Gibson DG. Relation of regional echo amplitude to left ventricular function and the electrocardiogram in left ventricular hypertrophy. *Br Heart J* 1984,52:99–105

7 Perez JE, Barzilai B, Madaras EI, *et al*. Applicability of ultrasonic tissue characterization for longitudinal assessment and differentiation of calcification and fibrosis in cardiomyopathy *J Am Coll Cardiol* 1984,4.88–95.

8 Miller JG, Perez JE, Sobel BE Ultrasonic characterization of myocardium *Prog Cardiovasc Dis* 1985,28 85–110.

9 Vered Z, Barzilai B, Mohr GA, *et al*. Quantitative ultrasonic tissue characterization with real-time integrated backscatter imaging in normal human subjects and in patients with dilated cardiomyopathy *Circulation* 1987,5 1067–73

10 Lythall DA, Gibson DG, Swanson K, Mitchell AG, Ilsley CD, Yacoub MH Quantitative analysis of myocardial echo amplitude—a useful marker of cardiac rejection [abstract] *Circulation* 1989,80(suppl II)·677

11 Madaras EI, Barzilai B, Perez JE, Sobel BE, Miller JG Changes in myocardial backscatter throughout the cardiac cycle. *Ultrason Imaging* 1983;5 229–39.

12 Olshansky B, Collins SM, Skorton DJ, Prasad NV Variation of left ventricular myocardial gray level on two-dimensional echocardiograms as a result of cardiac contraction. *Circulation* 1984,6.972–7.

13 Barzilai B, Madaras EI, Sobel BE, Miller JG, Perez JE Effects of myocardial contraction on ultrasonic backscatter before and after ischemia *Am J Physiol* 1984,247 H478–83.

14 Wickline SA, Thomas LJ III, Miller JG, Sobel BE, Perez JE A relationship between ultrasonic integrated back scatter and myocardial contractile function. *J Clin Invest* 1985;76 2151–60.

15 Bamber JC, Daft C Adaptive filtering for reduction of speckle in ultrasonic pulse-echo images *Ultrasonics* 1986; 5 41–4.

16 Massay RJ, Logan-Sinclair RB, Bamber JC, Gibson DG Quantitative effects of speckle reduction on cross sectional echocardiographic images *Br Heart J* 1989,62 298–304.

17 Corya BC, Rasmussen S, Feigenbaum H, Knoebel SB, Black MJ Systolic thickening and thinning of the septum and posterior wall in patients with coronary artery disease, congestive cardiomyopathy, and atrial septal defect. *Circulation* 1976,55(1).109–14.

18 Wickline SA, Thomas LJ III, Miller JG, Sobel BE, Perez JE. The dependence of myocardial ultrasonic integrated backscatter on contractile performance. *Circulation* 1985; 72(1) 183–92.

19 Glueck RM, Mottley JC, Miller JG, Sobel BE, Sobel JE Effects of coronary artery occlusion and reperfusion on cardiac-cycle dependent variation of myocardial ultrasonic backscatter *Circ Res* 1985,56 683–9

20 Wickline SA, Thomas LJ III, Miller JG, Sobel BE, Perez JE Sensitive detection of the effects of reperfusion on myocardium by ultrasonic tissue characterization with integrated backscatter *Circulation* 1986,74(2) 389–400.

21 Zhao M, Zhang H, Robinson TF, Factor SM, Sonnenblick EH, Eng C. Profound structural alterations of the extracellular collagen matrix in postischemic dysfunctional ("stunned") but viable myocardium *J Am Coll Cardiol* 1987,10 1322–34

22 Sagar KB, Pelc LE, Rhyne TL, Wann LS, Waltier DC Influence of heart rate, preload, afterload, and inotropic state on myocardial ultrasonic backscatter. *Circulation* 1988,77(2) 478–83

23 Hajduczki I, Jaffe M, Areeda J, *et al*. Ultrasonic backscatter and 2D echocardiographic wall motion during PTCA [abstract]. *Circulation* 1988,78(suppl II) 442

24 Milunski MR, Mohr GA, Perez JE, *et al* Ultrasonic tissue characterization with integrated backscatter acute myocardial ischemia, reperfusion, and stunned myocardium in patients. *Circulation* 1989,80 491–503

25 Milunski MR, Canter CE, Wickline SA, Sobel BE, Miller JG, Perez JE. Cardiac cycle dependent variation of integrated backscatter is not distorted by abnormal myocardial wall motion in human subjects with paradoxical septal motion. *Ultrasound Med Biol* 1989,15(4) 311–7

26 Aygen M, Popp RL Influence of the orientation of myocardial fibres on echocardiographic images *Am J Cardiol* 1987,60 147–52

27 Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH Left ventricular fibre architecture in man *Br Heart J* 1981,45.248–63

28 Streeter DD Jr, Spotnitz HM, Patel DP, Ross J Jr, Sonnenblick EH. Fibre orientation in the canine left ventricle during diastole and systole. *Circ Res* 1969, 24:339–47

29 Masuyama T, St Goar FG, Tye TL, Oppenheim G, Schnittger I, Popp RL. Ultrasonic tissue characterization of human hypertrophied hearts in vivo with cardiac cycle-dependent variation in integrated backscatter. *Circulation* 1989,80 925–34

30 Masuyama T, Nellessen U, Schnittger I, Tye TL, Haskell WL, Popp RL Ultrasonic tissue characterization with a real time integrated backscatter imaging system in normal and aging human hearts. *J Am Coll Cardiol* 1989,14· 1702–8

31 Lenkiewicz JE, Davies MJ, Rosen D Collagen in human myocardium as a function of age *Cardiovasc Res* 1972, 6:549–55

32 Weber KT. Cardiac interstitium in health and disease the fibrillar collagen network *J Am Coll Cardiol* 1989, 13(7).1637–52.

longitudinal fibres at this level.[27] By comparison the increased cyclic variation in distal regions of the canine left ventricle seen by Glueck *et al* [19] may reflect the higher proportion of longitudinal fibres and increased wall torsion at the apex.[28] Again relative fibre rearrangement within the myocardium during the cardiac cycle will influence the degree of wall thickening. Although the exact relation between myocardial systolic activity and cyclic variation is unclear, it is likely that both segmental myocardial contraction as evidenced by systolic thickening and cyclic variation in the ultrasound signal reflect conformational changes in contractile elements within the myocardium at either or both cellular and fibre levels.

Several workers who used integrated backscatter measurements for examining cyclic variation in the myocardial ultrasound signal have noted a disparity between systolic wall thickening and cyclic variation in both myocardial ischaemia and hypertrophy.[20 24 29] In their studies cyclic variation was determined as absolute change and did not incorporate any measure of background levels of ultrasound signal. Our use of the parietal pericardium as a method for standardising echo amplitude allows values of echo amplitude at end diastole and end systole to be assigned and enables the ratio of change in echo amplitude (cyclic variation index) to be calculated. Our results showed a considerable and significant improvement in correlation when the cyclic variation index rather than absolute change in echo amplitude was compared with systolic thickening. This suggests for example that a cyclic variation of 2 dB at a background end diastolic echo amplitude of 4 dB is associated with a greater degree of systolic wall thickening than a similar change of 2 dB at an end diastolic echo amplitude of 10 dB. We have previously shown that echo amplitude is increased in both left ventricular hypertrophy and ischaemic heart disease[5 6] and is associated with increased myocardial collagen in ischaemic heart disease and abnormalities of diastolic function such as diminished peak rate of wall thinning and cavity dimension increase in left ventricular hypertrophy. It is also known that the amplitude of the ultrasound signal depends on the angle between myocardial fibres and the ultrasound beam.[26] Because systolic wall thickening depends not only on intrinsic myocyte contraction but also on the interstitial collagen matrix and fibre realignment within the ventricular wall, it is not surprising that incorporating end diastolic echo amplitude, which reflects collagen and fibre alignment, enhances the correlation between cyclic variation and geometric indices of systolic activity such as wall thickening. This helps to explain some of the anomalies reported previously, such as significant cyclic variation in the presence of virtually absent wall thickening and motion as observed in infarcted and peri-infarcted areas of myocardium.[24] In that case end diastolic echo amplitude would be increased, resulting in a lower cyclic variation index compared with the observed absolute level of cyclic variation in decibels. However, as previous workers have shown and as this study confirms, the extent of cyclic variation is multifactorial and cannot be solely related to wall thickening. Of note in this study is the negative correlation between age and cyclic variation seen in the posterior wall of the ventricle which was not mirrored by a similar relation between age and systolic thickening. This is similar to that recently reported by Masuyama *et al* [30] and may reflect the many subtle changes in the myocardium which occur with aging, in particular the well documented increases in myocardial collagen.[31 32]

LIMITATIONS

There are several limitations to this study which must be considered. Although in this study subjects were generally good echo subjects, image quality as in most echocardiographic studies can be unsatisfactory. Full echo amplitude studies could not be analysed in three subjects. Also, owing to rotation and translation of the heart during the cardiac cycle, end systolic and end diastolic frames may not image directly comparable areas of myocardium. Simultaneous M mode and colour encoded images could not be obtained with the system we used and this may also introduce a source of error. Additionally the well known inaccuracies of M mode measurements particularly with respect to interventricular septal thickness must be considered. Finally, the present system still requires the master gain to be set using the parietal pericardial signals and this may introduce a small degree of subjectivity in overall values though not the extent of cyclic change.

CONCLUSIONS

Our observations in human subjects of a significant correlation between cyclic variation and systolic wall thickening strengthen the hypothesis that cyclic variation predominantly reflects local shortening within the myocardium. We have shown that there is a correlation between cyclic variation index and systolic wall thickening which is valid over a wide range of myocardial function and which is not altered by distorted wall motion. We also showed the importance of incorporating background echo amplitude into relations between cyclic variation in echo amplitude and systolic thickening. This emphasises the importance of having the capability to use in vivo standardisation which minimises the effect of the near field intervening tissue to enable relative levels of echo amplitude to be assigned. The clinical implications of this are that it may provide a non-invasive quantitative method for assessing segmental myocardial shortening which is sensitive to changes in contractility, local loading conditions, and local architecture. For example, this could be applied to determining the myocardium at risk during coronary angioplasty and the effect of interventions to limit this and the assessment of salvagable myocardium during thrombolytic therapy. In both, conventional geometric measurements of performance are limited by the distortion of wall motion in the peri-infarction or ischaemic zone. In these

Br Heart J 1991;66.277–80

Responsiveness of raised pulmonary vascular resistance to oxygen assessed by pulsed Doppler echocardiography

Michael Vogel, Jochen Weil, Heiko Stern, Konrad Bühlmeyer

Abstract

***Objective*—To assess whether changes in Doppler echocardiographic indices in the pulmonary artery correlated with changes in pulmonary vascular resistance.**

***Design*—Acceleration time, ejection time, maximal flow velocity, and velocity time integrals were measured at the same time as pressure and oxygen saturation measurements in room air and during 10 minutes of oxygen breathing in the catheterisation laboratory. Pulmonary vascular resistance and pulmonary blood flow (Qp) were calculated from catheterisation data by use of the Fick principle.**

***Patients*—14 consecutive patients with a congenital heart defect and a left to right shunt associated with raised pulmonary artery pressure who underwent routine diagnostic cardiac catheterisation to assess their pulmonary vascular resistance.**

***Results*—Though pulmonary vascular resistance and systolic pulmonary artery pressure fell significantly during oxygen administration, there was no significant change in the acceleration time or ejection time. Peak velocity increased significantly during oxygen administration. During oxygen breathing Doppler derived measurements of pulmonary flow showed a significant increase in Qp similar to the increase in Qp measured by the Fick principle. There was no significant correlation between the fall in pulmonary vascular resistance and the increase in acceleration time or ejection time, increase in peak velocity, increase in pulmonary artery diameter, or increase in Doppler derived pulmonary blood flow.**

***Conclusions*—Measurements of acceleration and ejection time by Doppler echocardiography did not predict the response of pulmonary artery pressure and resistance to oxygen. Though changes in maximal flow velocity across the pulmonary artery and in Doppler derived pulmonary blood flow measurements became significant during oxygen breathing, the correlation of these changes with fall in pulmonary vascular resistance was poor.**

Department of Pediatrics, Deutsches Herzzentrum, Munich, Federal Republic of Germany
M Vogel
J Weil
H Stern
K Buhlmeyer

Correspondence to
Dr Michael Vogel,
Deutsches Herzzentrum,
Lothstrasse 11, D-8000
Munich 2, Federal Republic
of Germany

Accepted for publication
14 May 1991

A prolonged increase in pulmonary artery flow and pressure can lead to the development of irreversible pulmonary vascular disease especially in children with large interventricular communications.[1] To judge soperability the standard technique is to measure pulmonary artery pressure and calculate pulmonary vascular resistance by the Fick method in the catheterisation laboratory.[1 2] Recently several studies have indicated that analysis of the pulmonary artery flow velocity profile by Doppler echocardiography may be a valuable non-invasive means of evaluating pulmonary artery pressure.[3-5] We evaluated the usefulness of Doppler echocardiography in assessing changes in pulmonary artery pressure and resistance after oxygen administration by comparing Doppler derived indices with simultaneous measurement of pulmonary artery pressure and calculation of pulmonary vascular resistance by the Fick principle during cardiac catheterisation.

Patients and methods

STUDY GROUP AND PATIENT SELECTION

We studied 14 children. All had raised pulmonary artery pressure as part of their congenital heart defect. Table 1 lists the diagnoses. Six children (patients 3, 5, 6, 7, 10 and 13) had Down's syndrome. Because sedated patients, especially those with Down's syndrome, can have altered pulmonary vascular resistance because of hypercapnia or acidosis,[2] we included only patients with a $P\text{CO}_2$ of <50 and a pH of $>7·34$. Because pulmonary vascular resistance varies spontaneously by up to 36% from day to day,[6] we only analysed data from patients whose change in pulmonary vascular resistance exceeded 40%.

Table 1 Clinical data on 14 patients with pulmonary artery hypertension

Patient	*Diagnosis*	*Age at time of study (yr)*
1	VSD, coarctation of the aorta	3·3
2	AVSD	0·5
3	AVSD	8·4
4	VSD	0·4
5	VSD	1·5
6	AVSD	0·5
7	AVSD	0·5
8	Mitral stenosis, subaortic stenosis, coarctation of the aorta	0·8
9	VSD	0·9
10	AVSD	1·1
11	VSD	0·2
12	VSD, coarctation of the aorta	0·6
13	AVSD	0·2
14	VSD, PDA	0·9

AVSD, atrioventricular septal defect, PDA, patent ductus arteriosus, VSD, ventricular septal defect.

ECHOCARDIOGRAPHIC METHODS

Commercially available equipment consisting of a Ultramark 8 or 9 imaging system by Advanced Technology Laboratories was used for the echocardiograms, which were obtained with either a 5 or 7·5 MHz transducer. The images were recorded on 1/2 inch videocasette tape. The echocardiographic study was performed in the cardiac catheterisation laboratory simultaneously while the patient was breathing room air and for 10 minutes while the patient was breathing 100% oxygen through a face mask. The Doppler flow in the pulmonary artery was analysed from the parasternal short axis view approximately 1 cm distal to the pulmonary valve. We used an offline computer (Kontron 200) to evaluate five consecutive cardiac cycles. The Doppler flow curve across the pulmonary artery was manually traced on the electronic drawing board with a light pen. The following variables were measured: peak velocity in the pulmonary artery (m/s); right ventricular ejection time (ET), from the onset of ejection to zero flow (ms); and acceleration time (AT), as the time interval from the onset of ejection to peak flow velocity (ms). Because AT and ET may be affected by changes in heart rate,[7 8] we also calculated the ratio AT/ET and the corrected AT obtained by dividing AT by the square root of the RR interval from the measurements mentioned above. The pulmonary systolic velocity time integral (VTI) was determined by digitising and integrating the area under the Doppler velocity curve according to the following equation: $VTI = \int ET \times pkV(t)\,dt$, where ET is the ejection time and pkV the instantaneous peak velocity. Pulmonary blood flow was calculated by multiplying the VTI by the luminal area of the pulmonary artery measured at the pulmonary valve level.[9]

CARDIAC CATHETERISATION

All children underwent cardiac catheterisation. Sedation consisted of morphine 0·1 mg/kg in combination with flunitrazepam 0·04 mg/kg given intramuscularily. Pressures were measured with standard fluid filled catheters coupled to a Statham transducer. We measured pulmonary and systemic blood flows by the Fick method using measured oxygen consumption and oxygen content derived from radiometer oxygen saturation. Mixed venous oxygen saturation was obtained from the superior and inferior venae cavae (SVC and IVC) and calculated as (3 × SVC) + (1 × IVC) saturation divided by four.[2] Pulmonary venous blood was obtained from the left atrium in eight patients and from a pulmonary vein in six. All pressure recordings and oxygen saturation samplings were performed before and at the end of a 10 minute period of breathing 100% oxygen by face mask. A Doppler echocardiographic study was performed at the same time. Pulmonary and systemic resistances were derived from the pressures and flows across the respective vascular beds. The ratio between pulmonary and systemic vascular resistance was also calculated and it was regarded as an important indicator of the responsiveness of the pulmonary vascular bed because errors in oxygen capacity cancel out[10] and use of the ratio avoids the need to index for flows and resistances.[2]

STATISTICAL ANALYSIS

Data are expressed as mean (SD). Linear regression analysis was used to determine the correlation between changes in pulmonary vascular resistance and Doppler derived variables. We used Student's paired *t* test to compare data. A p value of $<0·05$ was regarded as significant.

Results

Table 2 shows the results of the measurements before and during oxygen breathing of the pulmonary artery Doppler flow curve and pulmonary artery pressure during the cardiac catheterisation. Table 3 shows the changes in the pulmonary artery flow profile and measurements obtained at cardiac catheterisation during oxygen administration. The pulmonary vascular resistance and ratio of pulmonary vascular to systemic vascular resistance changed significantly, whereas there was no significant change in the acceleration or ejection time. Table 4 shows the changes in pulmonary artery luminal area and pulmonary blood flow determined either by Doppler echocardiography or by Fick principle during oxygen breathing.

Linear regression analysis showed no

Table 2 Cardiac catheterisation and Doppler echocardiographic data in 14 patients with pulmonary artery hypertension

	PA pressure (mm Hg)		*PA resistance ($U.m^2$)*		*Acceleration time (ms)*		*Acceleration time/RR*		*Ejection time (ms)*		*Acceleration/ ejection time*		*PA Doppler velocity (m/s)*	
Patient	*Room air*	*O_2*	*Room air*	*O_2*	*Room air*	*O_2*	*Room air*	*O_2*	*Room air*	*O_2*	*Room air*	*O_2*	*Room air*	*O_2*
1	103	100	17 2	10 1	48	63	1 9	2·7	138	154	0 35	0 41	0 48	0 64
2	78	55	2 9	0 3	75	97	3 7	4·9	203	193	0 37	0 5	1 61	1 52
3	65	48	9 4	1 1	99	115	3 8	4 0	225	246	0 44	0 46	0 96	0 71
4	70	67	3 5	1 5	116	94	6 0	5 2	214	231	0 54	0 4	1 41	1 66
5	78	55	2 1	0 1	65	102	3 4	4 7	113	263	0 57	0 39	0 78	1 11
6	75	81	4 1	3 3	53	97	2·7	4 3	177	222	0 30	0 42	0 75	1 27
7	72	72	3 0	0 6	100	111	4·8	5 4	234	266	0 43	0 42	1 26	1 64
8	108	88	18 0	11·5	94	89	5·7	4 0	207	224	0 45	0 40	0 65	0 74
9	76	74	14 5	6 0	74	109	3·2	4 7	193	194	0 56	0 56	0 63	0 85
10	73	71	2 7	0 9	69	101	3·5	4 3	211	236	0 33	0·43	1 23	1 22
11	74	65	7 1	1 1	107	111	5·4	5 4	212	214	0·50	0 52	1 40	1 71
12	75	69	10 8	5 1	66	110	2·9	5·5	140	178	0·47	0·62	0 71	1 08
13	74	56	5 1	0 9	112	113	5·9	5 9	220	200	0 56	0 57	1 53	1 80
14	78	65	6 2	2·1	130	82	6·2	4 2	242	220	0 54	0 37	1 29	1 42

PA, pulmonary artery.

Table 3 Doppler flow curve and cardiac catheterisation data before and during oxygen breathing in 14 patients with pulmonary artery hypertension

Variable	*Before*	*During*	*p Value*
AT (ms)	83 9 (26)	94 9 (28)	NS
Heart rate (beats/min)	136 6 (21)	131 6 (31)	NS
Corrected AT (ms)	3·9 (1·3)	4 3 (1)	NS
ET (ms)	184 2 (38)	203 8 (47)	NS
AT/ET	0 44 (0 08)	0 43 (0 08)	NS
Flow velocity (m/s)	0 97 (0·38)	1 08 (0 4)	0 05
PA pressure (mm Hg)	83 6 (17·9)	74·3 (18 6)	0 007
Qp/Qs	1·5 (1 1)	7 1 (6 8)	0 04
Rp (U.m²)	13·1 (12)	5·5 (5 1)	0 006
Ratio Rp/Rs	0 79 (0·75)	0·29 (0 31)	0 01

Pa, pulmonary artery; AT, acceleration time, ET, ejection time; Rs, systemic vascular resistance; Rp, pulmonary vascular resistance.

Table 4 Pulmonary artery diameter, VTI, and Qp determined before and during oxygen breathing by Doppler or Fick principle in 14 patients with pulmonary artery hypertension

	PA luminal area		*VTI*		*Qp by Doppler*		*Qp by Fick*	
Patient	*Before*	*During*	*Before*	*During*	*Before*	*During*	*Before*	*During*
1	2 7	4 0	4 6	10 3	2 1	2 5	4 0	6 4
2	1 6	1 8	16 1	20	4 0	4 4	3 0	6 6
3	3 0	3 3	12	16 9	3 8	3 9	3 0	5 4
4	1 6	1 7	16 3	21 2	3 9	6 6	2 4	5 1
5	0 7	0 9	5 7	15 5	0·7	1 8	2·6	22 0
6	0 8	0 9	18 8	30	2 2	4·4	3 4	8·1
7	1 4	1 5	16 4	20 3	3 0	4 1	2 7	4 8
8	1·6	1 9	6 3	8 7	1 5	2 0	2 6	3 1
9	1 8	2 1	5	6·7	1·1	1 3	3 1	6 7
10	1 4	1 7	11 4	19 4	2·7	4 2	2 1	4 3
11	0 9	1 6	16 7	22 5	2 1	5·4	2 6	5 7
12	1 9	2 4	6 3	10 4	1 7	2 9	1 4	2 5
13	0 2	0 5	18 3	24	1 9	2 0	1 8	4 6
14	0·8	0 8	17 5	17 5	1·9	2·1	1 8	2 2
p	p < 0 003		p < 0 001		p < 0 002		p < 0 01	

PA, pulmonary artery, VTI, velocity time integrals, Qp, pulmonary blood flow.

correlation between the fall in pulmonary vascular resistance during oxygen breathing and the increase in AT ($r = 0.22$; $p < 0.45$) or the AT corrected for heart rate ($r = 0.05$; $p < 0.84$), ET ($r = 0.42$; $p < 0.14$), AT/ET ($r = 0.1$; $p < 0.73$), increase of peak flow velocity across the pulmonary valve ($r = 0.2$; $p < 0.49$), increase in pulmonary artery luminal area ($r = 0.52$; $p < 0.06$), increase in velocity time intervals ($r = 0.55$; $p < 0.04$), or increase in pulmonary blood flow ($r = 0.42$; $p < 0.16$).

Discussion

Doppler echocardiography is safe, relatively easy to perform, and repeatable. It could be useful in clinical studies of congenital heart defects that increase pulmonary artery flow and pressure, because patients could be followed serially and their response, in terms of pulmonary vascular resistance, to oxygen or pulmonary vasodilator drugs estimated.

Initial reports about the specificity and sensitivity of measurements of acceleration and ejection time in distinguishing patients with abnormally high pulmonary artery pressure from those with normal pulmonary artery pressure were promising.[3-5] The results of some of these studies have recently been questioned. Drawbacks include the variability in Doppler flow curves attributable to differences in the pulmonary artery sampling site,[11] the inability of the method to detect moderate increases in pulmonary artery pressure,[12] and its inability to detect significant changes in pulmonary vascular resistance in response to pulmonary vasodilator treatment.[13]

Panidis *et al* reported considerable differences in acceleration time, ejection time, and maximal flow velocity across the pulmonary valve in controls with normal pulmonary artery pressure and in patients with increased pulmonary artery pressure when four different sampling sites were used: right ventricular outflow tract, pulmonary valve, centre of main pulmonary artery, and near the main pulmonary artery wall.[11]

In an animal study Gutgesell *et al* showed that the Doppler velocity flow indices were relatively insensitive to moderate increases in pulmonary artery blood flow or pressure.[12] In a clinical study in patients with primary pulmonary hypertension no significant difference in acceleration or right ventricular ejection time could be detected between a normal control group and patients in whom raised pulmonary artery pressure had been measured at a previous cardiac catheterisation.[13]

In a study of 21 children with ventricular septal defect 11 responded significantly to vasodilator drugs during cardiac catheterisation. There was no significant difference in terms of acceleration or right ventricular ejection time between responders and nonresponders.[13] In another study of six infants no difference was detected in the Doppler flow indices before and after oxygen breathing.[14]

Slight but significant changes in maximal pulmonary artery flow velocity in patients with pulmonary hypertension responsive to pulmonary vasodilator treatment have been reported.[13 15] One group noted that three patients with pulmonary obstructive disease and a poor response to vasodilator treatment had a flow velocity of <1 m/s and speculated that irreversible pulmonary hypertension can be assumed in a patient whose peak velocity remains <1 m/s after pulmonary vasodilation.[15] However, our data and the study from Cooper *et al*[13] do not support this assumption. Cooper *et al* found one patient with a peak pulmonary artery velocity of 1·24 m/s after vasodilator treatment whose lung biopsy specimen showed grade IV pulmonary vascular disease.[13] We successfully operated on a child (patient 9 in tables 1 and 2) whose velocity after oxygen administration was 0·85 m/s and whose pulmonary vascular resistance fell to 6 units $\times$ m^2, yielding a Rp/Rs ratio of 0·3 after oxygen breathing.

In all our patients pulmonary artery blood flow assessed by Doppler echocardiography increased significantly. This was in part due to an increase in the pulmonary artery luminal area. Again we could not show any positive correlation between an increase in Doppler flow across the pulmonary artery or an increase in pulmonary artery luminal area and the decrease of pulmonary vascular resistance.

The finding that Doppler flow velocity or velocity time integrals in the pulmonary artery are not reliable indicators of the reversibility of increased pulmonary vascular resistance is not surprising because the Doppler flow velocity curve is influenced by the sampling site in a similar way as the Doppler time indices.[16 17]

The clinical application of the pulsed Doppler method of assessing pulmonary resistance is further limited by the fact that the spontaneous variability in pulmonary blood flow is presumably increased in patients with primary pulmonary hypertension.[18] In this group spontaneous changes in pulmonary artery pressure of 22% and pulmonary vascular resistance of 36% have been reported.[6] Because of this high variability in pulmonary vascular resistance we excluded from our study those patients whose pulmonary vascular resistance fell less than 40% during oxygen administration. The high spontaneous variability of pulmonary vascular resistance also limits the applicability of cardiac catheterisation studies for the assessment of the responsiveness of pulmonary vascular resistance to oxygen.[15 19]

Published reports[12–14] and our data show that cardiac catheterisation remains the best method of assessing the potential reversibility of increased pulmonary vascular resistance.

This work was presented in part at the XXVI annual meeting of the Association of European Pediatric Cardiologists in Oslo, June 12–15th 1990.

1 Hoffman JIE Ventricular septal defect: indications for therapy in infants. *Pediatr Clin North Am* 1971;18: 1091–107
2 Morrison G, Macartney F. Effects of oxygen administration, bicarbonate infusions, and brief hyperventilation on patients with pulmonary vascular obstructive disease. *Br Heart J* 1979,41:584–93.
3 Kitabatake A, Inoue M, Asao M, Masuyama T, Tanouchi J, Morita T, *et al.* Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation* 1983;68:302–9.
4 Kostukaris D, Goldberg SJ, Allen HD, Loeber C. Doppler echocardiographic prediction of pulmonary arterial hypertension in congenital heart disease. *Am J Cardiol* 1984;53:1110–5.
5 Martin-Duran R, Larman M, Trugeda A, Vasquez de Prada JA, Ruano J, Torres A, *et al.* Comparison of Doppler-determined elevated arterial pressure with pressure measured at cardiac catheterisation. *Am J Cardiol* 1986;57:859–63.
6 Rich S, D'Alonzo GE, Dantzker DR, Levy PS Magnitude and implications of spontaneous hemodynamic variability in primary pulmonary hypertension. *Am J Cardiol* 1985;55:159–63.
7 Serwer GA, Cougle AG, Eckerd JM, Armstrong BE Factors affecting use of the Doppler-determined time from flow onset to maximal pulmonary artery velocity for measurement of pulmonary artery pressure in children *Am J Cardiol* 1986;58:352–6.
8 Gardin JM, Sato D, Rohan MK, Shu VWC, Allfie A, Gardin SK, *et al.* Effect of acute changes in heart rate on Doppler pulmonary artery acceleration time [abstract] *Circulation* 1986;74 (suppl II):II–180.
9 Goldberg SJ, Sahn DJ, Allen HD, Valdez-Cruz LM, Hoenecke H, Carnahan Y. Evaluation of pulmonary and systemic blood flow by 2-dimensional Doppler echocardiography using fast Fourier transform spectral analysis. *Am J Cardiol* 1982;50:1394–400.
10 Krongard E, Helmholz H Jr, Ritter DG. Effect of breathing oxygen in patients with severe pulmonary vascular obstructive disease *Circulation* 1973;47:94–100
11 Panidis I, Ross J, Mintz GS. Effects of sampling site on assessment of pulmonary artery blood flow by Doppler echocardiograpy. *Am J Cardiol* 1986;58·1145–7
12 Gutgesell H, Kaul S, Ohner J, Kelly P. Influence of heart rate, pulmonary blood flow and pulmonary artery pressure on the Doppler-derived pulmonary flow velocity pattern [Abstract]. *Circulation* 1986;74 (suppl II):II–381.
13 Cooper MJ, Tyndall M, Silverman NH. Evaluation of the responsiveness of elevated pulmonary vascular resistance in children by Doppler echocardiography *J Am Coll Cardiol* 1988;12.470–5.
14 Ritter SB, Cooper RS, Golinko RK. Non-invasive assessment of pulmonary vascular reactivity in congenital heart disease: pulsed Doppler application. *J Cardiovasc Ultrason* 1986;5:213–21.
15 Tomita H, Nakaya S, Futaki S, Nakajima T, Arakaki Y, Kamiya T. Non-invasive evaluation of the pulmonary vascular resistance by pulsed Doppler echocardiography. In: Doyle EF, Engle MA, Gersony W, Rashkind WG, Talner NS, eds. *Pediatric cardiology. proceedings of the second world congress.* New York. Springer Verlag, 1985 91–4
16 Meijboom EJ, Risterborgh H, Bot H, de Boo J, Roelandt J, Bom N. Limits of reproducibility of blood flow measurements by Doppler echocardiography. *Am J Cardiol* 1987,59:133–7
17 Chan K-L, Currie PJ, Seward JB, Hagler DJ, Mair DD, Tajik AJ. Comparison of three Doppler ultrasound methods in the prediction of pulmonary artery pressure. *J Am Coll Cardiol* 1987;9:549–54.
18 Friedman DM, Bierman FZ, Barst R. Gated pulsed Doppler evaluation of idiopathic pulmonary artery hypertension in children. *Am J Cardiol* 1986;58:369–70.
19 Schuster AH, Nanda NC. Doppler echocardiographic measurement of cardiac output. comparison with a non-golden standard *Am J Cardiol* 1984;53:257–9.

Br Heart J 1991;66:281–4

Transoesophageal echocardiographic assessment of fixed subaortic obstruction in children

J P Gnanapragasam, A B Houston, W B Doig, M P G Jamieson, J C S Pollock

Abstract

***Objective*—To evaluate the clinical usefulness of transoesophageal echocardiography in the assessment of children with fixed left ventricular outflow tract stenosis.**

***Patients and methods*—Eight consecutive children, aged over 5 years, with fixed subaortic stenosis and one child with fixed subpulmonary left ventricular outflow tract stenosis were prospectively assessed by precordial and transoesophageal echocardiography.**

***Results*—Transoesophageal images of the left ventricular outflow tract were much clearer than precordial images in all patients except one with a prosthetic mitral valve. Improved visualisation provided further information on the nature of the lesion (additional chordal attachment of the mitral valve in one, accessory atrioventricular valve tissue with aneurysm formation in one), on the extent of the lesion (circumferential in three), and on the very close relation of a ridge to the aortic valve leaflets in one. Transoesophageal Doppler did not provide any additional information on aortic regurgitation and was unreliable for gradient estimation across the left ventricular outflow tract.**

***Conclusions*—Transoesophageal imaging provides an excellent means of visualising lesions in the left ventricular outflow tract and can be useful in a few children and adolescents in whom precordial echocardiography does not provide adequate information. The technique can also be used intraoperatively to define the full extent of the obstructive lesion and to assess residual lesions after surgery.**

Departments of Cardiology and Cardiac Surgery, Royal Hospital for Sick Children, Glasgow
J P Gnanapragasam
A B Houston
W B Doig
W P G Jamieson
J C S Pollock

Correspondence to
Dr J P Gnanapragasam,
Department of Cardiology,
Royal Hospital for Sick Children, Glasgow G3 8SJ.

Accepted for publication
10 May 1991

Fixed subaortic stenosis is a relatively uncommon cause of obstruction to the outflow of the left ventricle but is important because it requires earlier intervention than in aortic valve stenosis. The nature of the lesion, its circumferential extent, and its relation to the aortic valve leaflets can vary. Precordial echocardiography, currently the investigation of choice in these patients, will identify a subaortic lesion in most children but may fail to show it in a few.[1] Transoesophageal echocardiography permits clear visualisation of lesions of the left ventricular outflow tract and has been reported to be useful in adults with inconclusive precordial findings.[2 3] The technique usually requires general anaesthesia in children and any benefits have to be balanced against this. We report our experience when we used this technique to assess left ventricular outflow tract obstruction in children.

Patients and methods

Eight consecutive children, aged over 5 years, with fixed subaortic obstruction were assessed. During the study period a child presented with fixed subpulmonary obstruction in the presence of transposition of the great arteries and was also included in the assessment. We excluded children aged < 5 because a standard (adult) sized transducer was used for the transoesophageal study. Table 1 shows the ages and details of previous surgery. All patients were symptom free but had physical signs of left ventricular outflow obstruction, and two (patients 3 and 6) also had the murmur of aortic regurgitation. All were assessed initially by precordial imaging and Doppler echocardiography and five were referred for surgery without further investigations. Three patients underwent cardiac catheterisation. A patient with recurrent subaortic stenosis and poor precordial views underwent cardiac catheterisation before surgery (patient 1). Patient 2 who had a bicuspid aortic valve and a prosthetic mitral valve was catheterised to better define the site and severity of obstruction and underwent a transoesophageal study at the same time. Patient 9 had a baffle leak and pulmonary venous obstruction after Mustard repair and

Table 1 Age at transoesophageal echocardiography (TOE) and details of previous surgery

Patient	*Age at TOE study*	*Previous surgery (age)*
1	13 yr 4 month	Repair of atrioventricular septal defect and resection of subaortic ridge (3 yr 10 month)
2	5 yr 2 month	Repair of coarctation (6 days) Mitral valve replacement (2 yr 3 month)
3	12 yr 2 month	Repair of coarctation (8 yr 9 month) Resection of subaortic ridge (9 yr 7 month)
4	6 yr	None
5	14 yr 10 month	None
6	9 yr 7 month	Ligation of ductus arteriosus (4 yr 10 month)
7	7 yr 5 month	None
8	5 yr 5 month	None
9	7 yr 3 month	Mustard procedure (3 yr 10 month)

Table 2 Precordial and transoesophageal echocardiographic findings in nine patients

Patient	*Precordial findings*	*Transoesophageal findings*
1	Poorly defined projection on posterior aspect of LVOT LVOT gradient 75 mm Hg AR	Prominent accessory atrioventricular valve tissue and a small ridge over the septum Gradient not measurable AR
2	Bicuspid aortic valve Prosthetic mitral valve projecting into LVOT Small projection over septum LVOT gradient 100 mm Hg AR	Shadow of prosthetic valve masking LVOT Gradient not measurable AR
3	Small subaortic ridge just below aortic valve LVOT gradient 85 mm Hg AR	Circumferential ridge at site of insertion of valve leaflets Gradient not measurable AR
4	Subaortic shelf clearly seen on septal aspect of LVOT LVOT gradient 65 mm Hg	Smaller shelf on mitral aspect forming a circumferential ridge Gradient not measurable
5	Ridge over septum LVOT gradient 70 mm Hg AR	No additional findings Gradient not measurable AR
6	Circumferential ridge more prominent over septum LVOT gradient 70 mm Hg AR	No additional findings Gradient not measurable AR
7	Circumferential ridge more prominent over septum LVOT gradient 100 mm Hg AR	No additional findings Gradient not measurable AR
8	Circumferential subaortic ridge LVOT gradient 80 mm Hg AR	No additional findings Gradient not measurable AR
9	Small ridge over mitral and septal aspects of LVOT LVOT gradient 70 mm Hg	Additional chordal attachment of mitral valve to septum Gradient not measurable

LVOT, left ventricular outflow tract; AR, aortic regurgitation.

underwent cardiac catheterisation to assess the state of the baffle before surgery. Transoesophageal echocardiography was performed as a primary diagnostic procedure in a patient with recurrent subaortic stenosis in whom the precordial images were an inadequate basis for a decision on re-operation (patient 3). Seven patients have so far undergone surgery and all had intraoperative transoesophageal studies.

The echocardiographic studies were performed with a Vingmed 700 ultrasound machine. We used a 5·0 MHz frequency standard (adult) sized transoesophageal transducer with facilities for transverse plane imaging, and pulsed, continuous wave, and colour Doppler. The left ventricular outflow tract was viewed by angulation of the oesophageal transducer to obtain a long axis view of the left ventricle.[4] Surgical confirmation of the lesion was possible in the seven patients who had surgery.

Results

The studies were assessed to determine whether the transoesophageal technique gave more information than the precordial technique.

COMPARISON OF TRANSTHORACIC AND TRANSOESOPHAGEAL ECHOCARDIOGRAPHY FINDINGS

Table 2 shows the findings obtained by the two methods.

Imaging

In patient 1 who was obese and had very poor precordial images transoesophageal echocardiography clearly showed accessory atrioventricular valve tissue which formed a blood filled aneurysm in the left ventricular outflow tract during systole and also showed a slight ridge over the septum (fig 1). The transoesophageal demonstration of this lesion was also much better than the angiographic images obtained in this patient. In the patient with the fixed subpulmonary obstruction transoesophageal imaging showed that an unsuspected additional chordal attachment of the mitral

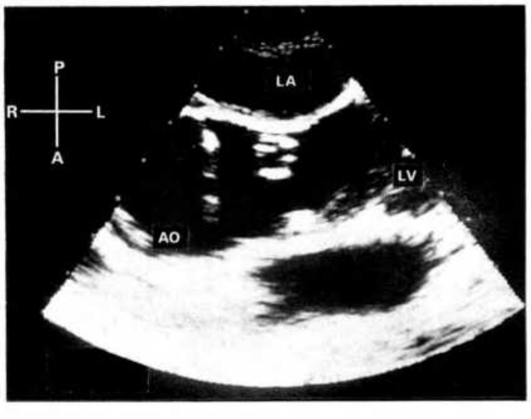


Figure 1 Transoesophageal echocardiogram clearly showing prominent accessory left atrioventricular valve tissue which looked like a cyst in systole and collapsed in diastole and also showing a slight ridge over the septum (patient 1). LA, left atrium; LV, left ventricle; AO, aorta.

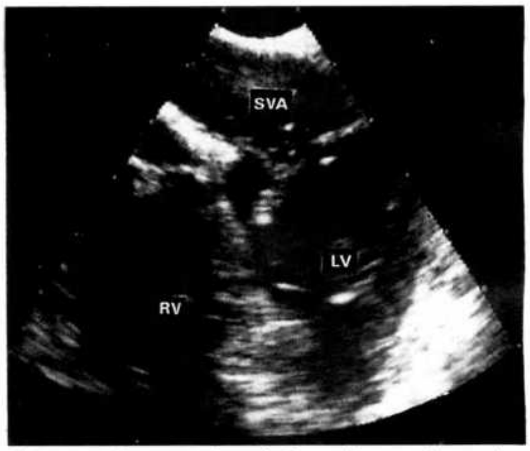


Figure 2 Transoesophageal echocardiogram (long axis view) of the left ventricle in patient 9 showing additional chordal attachment of the mitral valve to the left ventricular outflow tract. SVA, systemic venous atrium; LV, left ventricle; RV, right ventricle.

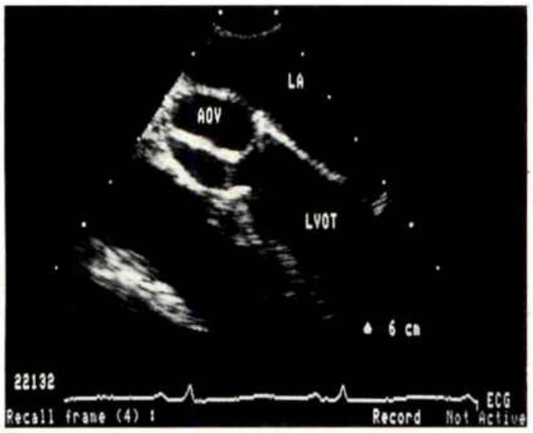


Figure 3 Transoesophageal echocardiogram showing the very close relation of the recurrent subaortic ring to the insertion of the aortic valve leaflets (patient 3). LA, left atrium; AOV, aortic valve; LVOT, left ventricular outflow tract.

valve obstructed flow through the left ventricular outflow tract (fig 2). The very close attachment of the recurrent subaortic ridge to the undersurface of the aortic valve leaflets was much better shown by transoesophageal imaging in patient 3 (fig 3). Transoesophageal echocardiography showed the circumferential nature of the obstruction in patient 4—that is, the smaller ridge on the mitral side as well as the prominent ridge on the septum seen by precordial imaging. No additional diagnostic information was provided by transoesophageal echocardiography in four other patients though the obstructive lesions were much more clearly shown (fig 4). In the patient with a mitral valve prosthesis (patient 2) transoesophageal viewing of the left ventricular outflow was limited owing to shadowing by the prosthetic valve and no additional information was obtained.

Doppler

A precordial view showed the maximum velocity across the left ventricular outflow tract in all patients by continuous wave Doppler when the position and direction of the transducer was adjusted to give a complete spectral signal showing the highest velocity. This could not be reliably determined by the oesophageal route because the Doppler beam could not be aligned with flow through the left ventricular outflow tract in any patient. Aortic regurgitation was detected by both transoesophageal and precordial Doppler in seven patients.

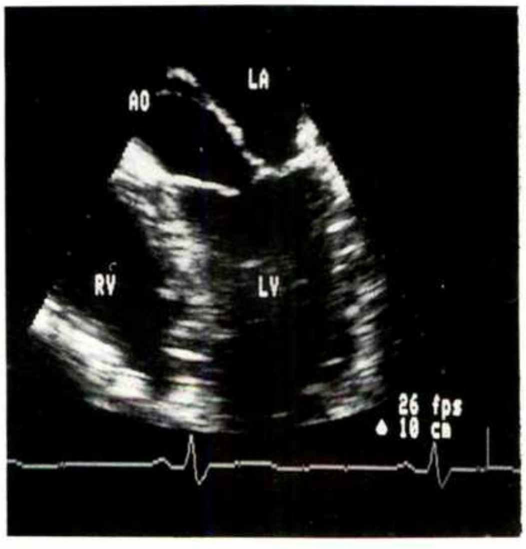


Figure 4 Transoesophageal echocardiogram (long axis view) of the left ventricle in a 14 year old showing a very prominent subaortic shelf projecting into the left ventricular outflow tract in systole (patient 6). LA, left atrium; LV, left ventricle; AO, aorta; RV, right ventricle.

Postoperative transoesophageal echocardiography studies

Intraoperative transoesophageal imaging after surgery and discontinuation of bypass showed complete resection of the ridge in all cases except patients 1 and 9. A small projection remained on the mitral aspect of the left ventricular outflow tract in patient 1 but because the fibromuscular tissue had been extensively resected and the left ventricular outflow tract appeared widely patent the result was considered acceptable. A small ridge remained on the septum in patient 9, in whom the small accessory papillary muscle was resected through a pulmonary arteriotomy, but there was no evidence of mitral regurgitation. During resection of the subaortic ridge in patient 8 the anterior leaflet of the mitral valve was breached and was oversewn with a single suture. Postoperative colour Doppler echocardiography showed a small colour jet of mitral regurgitation from the point of coaption of the mitral leaflets (as had been noted preoperatively) and no leak through the sutured region of the valve. Postoperative colour Doppler examination also showed persistence of aortic regurgitation in seven patients as noted preoperatively.

Discussion

The presence of a subaortic ridge can be confirmed by precordial echocardiography in most children.[1] In a few patients, however, image definition may not be good enough to allow a decision on surgery. Cardiac catheterisation can be undertaken in such cases but angiographic demonstration of the lesion can also be poor if the shelf is thin.[5]

In our series transoesophageal echocardiography provided excellent images of the left ventricular outflow tract in all patients except one with a prosthetic mitral valve. The clarity of the images obtained led to an accurate definition of the nature of the obstructive lesion, its circumferential extent across the left ventricular outflow tract, and its relation to the aortic valve leaflets. This technique is not reliable for gradient estimation because the left ventricular outflow tract is obliquely orientated in relation to the oesophagus and it is difficult to align a Doppler beam from the oesophagus parallel with the jet caused by the subaortic obstruction, which is often eccentric. The gradient can be easily estimated by precordial Doppler, however. The presence of physical signs of left ventricular outflow obstruction together with precordial echocardiographic confirmation of the lesion is sufficient for most children to proceed to surgery because discrete subaortic stenosis is a progressive lesion that leads to damage to the aortic valve and left ventricular myocardium.[5] A transoesophageal study under general anaesthesia is therefore not required to obtain further information before surgical referral in most children. Intraoperative use of this technique can nevertheless be valuable in defining the full extent of the lesion before surgery and detecting residual lesions and assessing function of the mitral valve after surgery. Intraoperative epicardial echocardiography has recently been reported to be valuable in the same situation.[6]

Long term follow up is necessary after surgery because the obstruction recurs in up to 27% of patients.[7] Precordial images of recurrent lesions in adolescents may not be as satisfactory as those obtained in younger children and transoesophageal echocardiography can be useful in this group of patients. In one of our adolescent patients (patient 1) with poor precordial images transoesophageal echocardiography showed the obstructive lesion better than angiography. In patient 3 transoesophageal echocardiography was helpful in defining the attachment of the small recurrent circumferential ridge to the undersurface of the insertion of the aortic valve leaflets (fig 3). Because further resection of the subaortic ridge could have damaged the aortic valve leaflets and led to valve replacement and because the patient was symptom free surgery was deferred. We believe that transoesophageal echocardiography rather than cardiac catheterisation is the preferred method of demonstrating a subaortic lesion if standard echocardiography does not provide sufficient information.

Transoesophageal echocardiography permits improved assessment of the nature and extent of lesions of the left ventricular outflow tract and can be of use in the few children in whom precordial echocardiography is inadequate for a management decision. In most children with left ventricular outflow tract obstructions transoesophageal echocardiography is not essential for preoperative diagnosis and its main role is in the intraoperative assessment.

JPG is supported by a grant from the Equipment Evaluation Committee of the Scottish Home and Health Department. We thank Mr E Murtagh and Mr S Lilley for their technical assistance

1 Motro M, Schneeweiss A, Shem-Tov A, *et al.* Two dimensional echocardiography in discrete subaortic stenosis. *Am J Cardiol* 1984;53·896–8.

2 Schwinger ME, Kronzon I Improved evaluation of left ventricular outflow tract obstruction by transesophageal echocardiography. *J Am Soc Echocardiogr* 1989;2:191–4.

3 Mugge A, Daniel WG, Wolpers HG, Klopper JW, Lichtlen PR. Improved visualisation of discrete subvalvular aortic stenosis by transoesophageal color-coded Doppler echocardiography. *Am Heart J* 1989;117:474–6.

4 Seward JB, Khandheria BK, Oh JK, *et al.* Transoesophageal echocardiography: technique, anatomic correlations, implementation, and applications. *Mayo Clin Proc* 1988; 63:649–80.

5 Somerville J. Aortic stenosis and incompetence. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds *Paediatric cardiology*. Edinburgh· Churchill Livingstone, 1987:987–92.

6 Sreeram N, Sutherland GR, Bogers JJC, *et al.* Subaortic obstruction. intraoperative echocardiography as an adjunct to operation. *Ann Thorac Surg* 1990,50:579–85

7 Stewart JR, Merrill WH, Hammon JW, Graham TP, Bender HW. Reappraisal of localized resection for subvalvar aortic stenosis. *Ann Thorac Surg* 1990,50 197–203.

Br Heart J 1991;66:285–9

Assessment of right and left ventricular function in terms of force development with gestational age in the normal human fetus

Martin St John Sutton, Tom Gill, Ted Plappert, Daniel H Saltzman, Peter Doubilet

Cardiovascular Division, Department of Medicine, Department of Radiology, Department of Obstetrics and Gynaecology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
M St John Sutton
T Gill
T Plappert
D H Saltzman
P Doubilet

Correspondence to
Dr Martin St John Sutton,
Cardiovascular Division,
Royal Brompton National
Heart and Lung Hospital,
Sydney Street, London SW3
6NP

Accepted for publication
29 April 1991

Abstract

Objective—**To assess right and left ventricular systolic function in normal human fetuses by cross sectional Doppler echocardiography to calculate the force developed by myocardial shortening.**

Design—**Cross sectional echocardiographic images of the aorta and pulmonary arteries were obtained prospectively in order to measure great vessel diameters and calculate their cross sectional areas. Doppler velocity signals were recorded from the proximal aorta and the proximal pulmonary artery and digitised to obtain peak velocity, acceleration time, flow velocity time integral during acceleration, and the flow velocity time integral for the whole of ejection. Right and left ventricular force development was estimated by Newton's equation in which force is defined as the product of mass and acceleration.**

Patients—**58 normal human fetuses at a gestational age of from 20 to 42 weeks.**

Results—**The cross sectional area of the pulmonary artery was 20% greater than that of the aorta. Aortic acceleration time was longer than that in the pulmonary artery, and peak blood flow velocity in the aorta was consistently greater than that in the pulmonary artery. Right ventricular stroke volume was significantly greater than left ventricular stroke volume. The force developed by the right and left ventricles was, however, similar throughout the gestational period studied, increasing tenfold from 20 weeks' gestation to term ($r = 0.74$, $p < 0.0001$; $r = 0.75$, $p < 0.0001$) respectively.**

Conclusion—**The development of right and left ventricular force in the human fetus is similar in spite of the greater volume handled by the right ventricle. This index of ventricular performance does not require calculation of ventricular volume and because it varies independently of ventricular geometry and heart rate it should prove useful in assessing cardiac function in the normal human fetus and in fetuses with ventricular dysfunction.**

Assessment of right and left ventricular function in terms of ejection fraction is not feasible in the human fetus because ventricular chamber volumes are too small to quantify accurately. Currently the only available measures of ventricular function in the human fetus are percent systolic shortening of the right and left ventricular short axis diameters and estimation of ventricular stroke volumes with cross sectional Doppler echocardiography.[1–5] Often it is not possible to assess ventricular systolic shortening because the ultrasound beam cannot be correctly aligned to pass through the right and left ventricular diameters. Moreover, although stroke volume can be calculated in most fetuses, it varies inversely with heart rate[6 7] and does not provide information regarding the efficiency of ventricular emptying.

A non-invasive method of assessing right and left ventricular function would be useful not only in normal human fetuses but more importantly in fetuses with ventricular dysfunction caused by Rhesus incompatibility, hypoxaemia, and recurrent tachycardias.[8] In addition, such a technique would be of value for early detection of the adverse cardiovascular effects of tocolytic β sympathomimetic agents which have become the mainstay treatment for prevention of premature birth.[9]

We describe a method of measuring right and left ventricular function in the human fetus in terms of myocardial force development that does not require estimation of ventricular volumes and is independent both of ventricular configuration and cardiac cycle length over the range of heart rates encountered.

This study had three aims: first to calculate the force developed by the two ventricles, second to assess the magnitude of changes in ventricular performance with gestational age, and third to determine whether there were any systematic differences between the two ventricles.

Patients and methods

STUDY POPULATION

We studied 58 normal fetuses whose mothers were recruited from patients referred for routine ultrasound examination. The indications for ultrasound examination were estimation of gestational age and placental location. Mothers with diabetes, hypertension, eclampsia, Rhesus incompatibility, and multiple gestations were excluded. Doppler echocardiograms were obtained from fetuses ranging in gestational age from 20 to 42 weeks. The study protocol was approved by the Brigham and Women's Hospital Human Subjects Com-

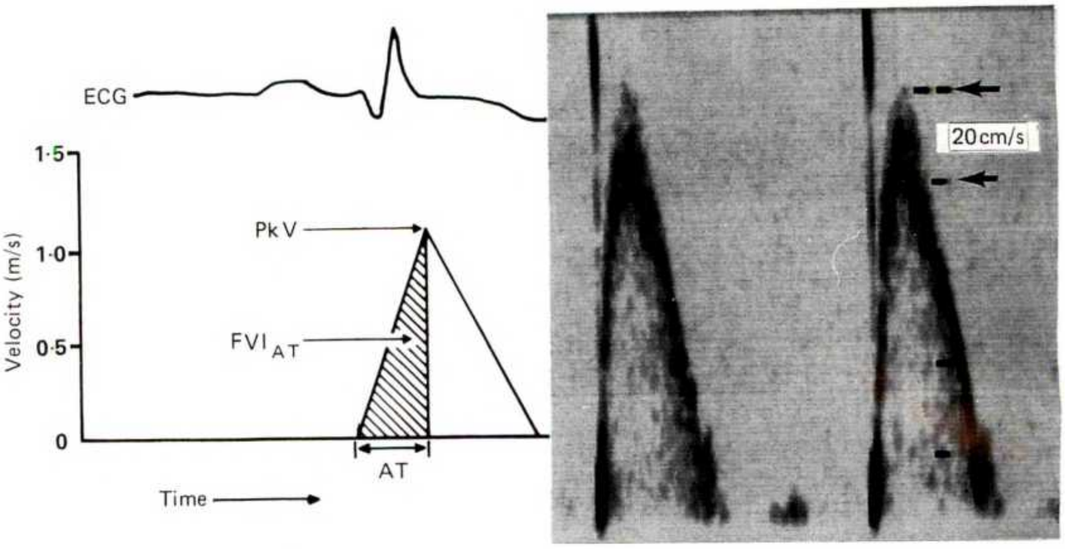


Figure 1 Doppler velocity signal from the aorta shown with schematic electrocardiogram. AT, acceleration time; PkV, peak velocity; FVI_{AT}, *blood velocity integral during acceleration.*

mittee of Harvard Medical School and written informed consent was obtained from each mother.

DATA ACQUISITION

Cross sectional Doppler echocardiographic studies were performed with a Hewlett Packard ultrasound system and a 3·5 MHz or more often a 5·0 MHz transducer. Each mother rested in the recumbent position for 15 minutes then a transducer was placed on her abdomen and the fetal heart was located using the fetal spine and liver as easily recognisable landmarks. A systematic cross sectional echocardiographic examination of the fetal heart was performed to exclude any structural abnormality and to confirm the presence of normal atrial situs, concordant atrioventricular connections, concordant ventriculoarterial connections, and normal cardiac chamber sizes and functions. The great arteries were identified by their characteristic pattern of major branches.

High quality cross sectional echocardiographic images of the aorta and pulmonary artery were obtained with the ultrasound beam aligned as orthogonally as possible with the axial plane of the vessels to measure their diameters. Doppler blood flow velocity signals were recorded from the main pulmonary artery and from the ascending aorta immediately distal to the respective semilunar valves. The pulsed wave Doppler sample volume was positioned within the lumen of the pulmonary artery and aorta and its size adjusted to sample velocities from the whole of the flow stream. The insonating beam was aligned as close as possible to parallel the direction of blood flow. The flow direction cursor was used to measure the angle of incidence between the ultrasound beam and the direction of blood flow, and Doppler velocity signals were only recorded when this was less than 20°. We chose 20° as a cut off because flow velocity varies inversely with the cosine of the angle of incidence, and velocity measured at an angle of 20°C underestimates true velocity by no more than 8%. Doppler signals with maximum velocity were recorded during periods of apnoea because fetal respiratory efforts can alter velocity amplitude.[10 11]

Heart rate was measured from the Doppler velocity signals obtained from the great arteries.

The gestational age of each fetus was assessed from the first day of the last menstrual period and corroborated by ultrasound measurements of biparietal cephalic diameter.[12 13]

DATA ANALYSIS

Cross sectional echocardiographic images of the aorta and pulmonary artery were transferred from half inch videotape to the digital disc of a Frieland Medical off-line computer analysis system. The aortic and pulmonary artery diameters were measured at the level of the annulus immediately distal to the semilunar valves at the time of maximum leaflet separation. The gain controls of the ultrasonoscope were adjusted to minimise "blooming" of echoes from the vessel walls. Measurements were made with an electronic cursor from a minimum of five separate cardiac cycles and rounded off to the nearest millimetre. Mean values were calculated for each vessel diameter.

Cross sectional areas of the pulmonary artery and of the aorta were calculated assuming a circular cross section $CSA = \pi(D/2).^2$ Doppler velocity signals recorded from the aorta and pulmonary artery from a minimum of three consecutive cardiac cycles during periods of fetal apnoea were transferred from videotape to the hard disc of the computer analysis system. The velocity spectral envelopes with the maximum velocities were digitised through the middle of the densest portion of the spectral envelope. The following measurements were made from the pulmonary artery and the aorta: (*a*) Peak velocity (pkV); (*b*) acceleration time (AT), defined as the time from the initial increase in velocity to the time of peak velocity. (fig 1); (*c*) the flow velocity time integral during acceleration (FVI_{AT}), which is the area under the velocity spectral envelope up to the time of peak velocity (fig 1); and (*d*) total velocity time integral FVI for the whole of ejection.

The force developed by each right and left ventricular contraction accelerated a column of blood into the pulmonary artery and aorta respectively and represented transfer of the

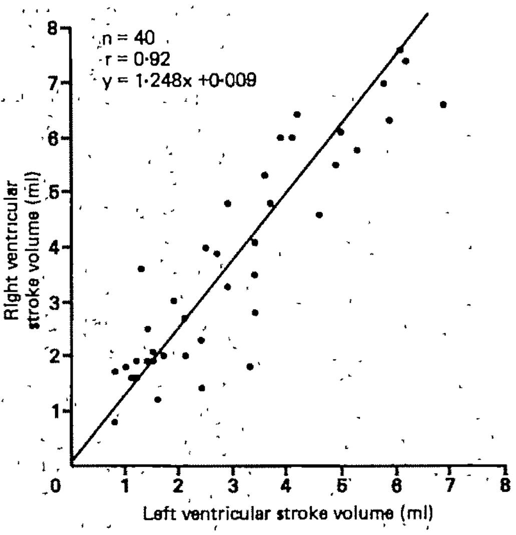


Figure 2 Comparison of right and left ventricular stroke volumes showing that for the population as a whole the right ventricular stroke volume was greater than left ventricular stroke volume.

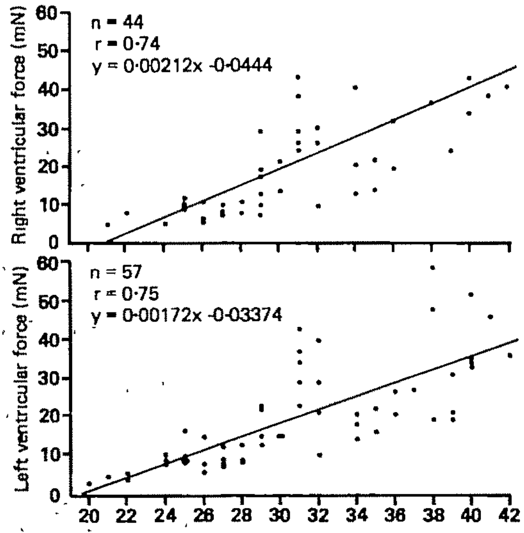


Figure 4 Plots showing a linear increase in right and left ventricular force with gestational age.

energy of myocardial shortening to work done on the pulmonary and systemic circulations. We used Newton's equation to estimate the force (that is, the product of mass and acceleration (F = ma)).[14] The mass component of the force equation was the mass of blood accelerated into the arteries, which was calculated as the product of the density of blood (1·055), the cross sectional area of the great artery (CSA), and the flow velocity time integral during acceleration (FVI_{AT}) (fig 1). The acceleration component of the force equation was estimated as the peak velocity divided by the acceleration time (pkV/AT)—thus force, F = (1·055 × CSA × FVI_{AT}) × (pkV/AT).

Right and left ventricular stroke volumes (SV) were calculated as the products of the cross sectional areas of the great arteries (CSA) and the flow velocity time integrals (FVI) of the Doppler signals obtained from the respective great arteries, so that SV = (FVI × CSA).

STATISTICAL ANALYSIS

Student's *t* test was used to assess the significance of differences between right and left ventricular force development, stroke volumes, peak velocities, aortic and pulmonary cross sectional areas, and acceleration times. Values are given as mean (1 SD).

We assessed changes in myocardial force development and stroke volume with gestational age and changes in right and left ventricular force and stroke volumes with gestational age by regression analysis using Pearson's method.

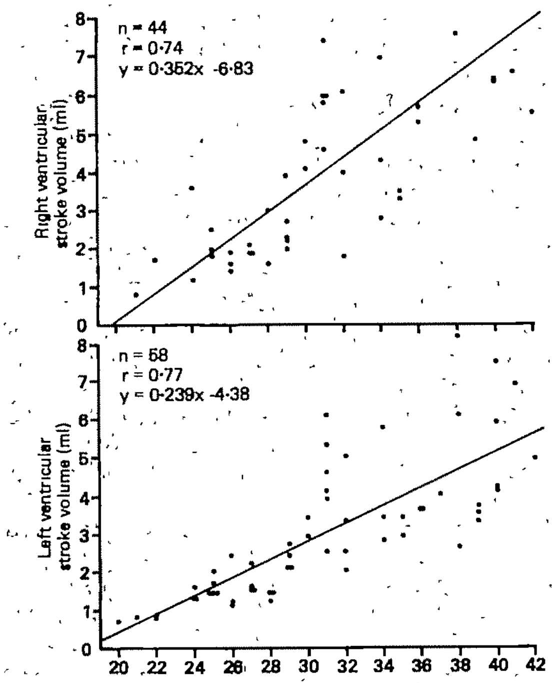


Figure 3 Plot showing a linear increase in right and left ventricular stroke volumes with gestational age.

Results

Pulmonary artery diameters were larger than aortic diameters throughout the period of gestation studied, so that the mean cross sectional

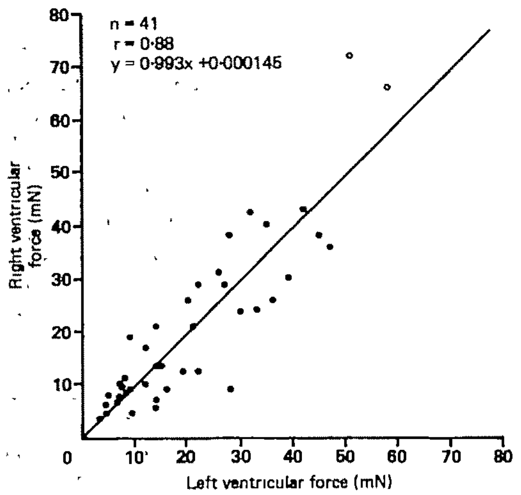


Figure 5 Plot comparing right and left ventricular force development and showing similar force development in the right and left ventricles

area of the pulmonary artery was 20% greater than that of the aorta (0·31 (0·16) cm^2 *v* 0·39 (0·20) cm^2) ($p < 0.01$). The blood flow velocities in the aorta were consistently greater than velocities in the pulmonary artery (mean 0·88 (0·14) m/s *v* 0·78 (0·13) m/s.) ($p < 0.0001$). However, neither the aortic nor the pulmonary artery peak velocities varied significantly with heart rate ($r = -0.01$, $r = +0.04$ respectively).

The mean ventricular stroke volume ejected by the right ventricle was 24% greater than that ejected by the left ventricle for the population as a whole (4·1 (2·6) ml *v* 3·3 (2·0) ml) ($p < 0.01$) (fig 2). Both right and left ventricular stroke volumes increased progressively with gestational age (fig 3). Heart rate declined from a mean of 144 beats per minute at 20 weeks to a mean of 129 beats per minute at 42 weeks. The acceleration time in the aorta was significantly longer than that in the pulmonary artery (44·6 (6·9) ms *v* 39·4 (10·6) ms) ($p < 0.001$).

The myocardial force developed by the right and left ventricles increased more than tenfold from 20 weeks' gestation to term, ($r = 0.74$, $p < 0.0001$; $r = 0.75$, $p < 0.0001$) (fig 4). The force developed by the right ventricle was similar to that developed by the left ventricle throughout the period of gestation studied (fig 5). The force developed by both ventricles varied independently of heart rate ($r = -0.12$ and $r = -0.11$).

REPRODUCIBILITY

The reproducibility of measurements of great vessel diameters in the human fetus has already been reported and the consequences of errors in diameter measurement on volume flow calculations derived from them have been estimated.[15]

Discussion

The lack of a simple measure of ventricular performance in the human fetus prompted us to develop a non-invasive technique to measure the force developed by both right and left ventricles. We chose to measure ventricular force because it can be defined in physical terms and because it relates directly to myocardial systolic shortening. Importantly, myocardial systolic shortening, force development, and the force-velocity relations in the fetal myocardium differ from those in the adult myocardium.[16] These differences in myocardial mechanics are determined by the different enzyme kinetics of the myosin ATP'ase on the fetal and adult myosin isoforms.[17 18]

We estimated force as the product of mass and acceleration as defined in Newton's equation. This required simple measurements of blood flow velocity signals and great artery diameters, all of which have been reported individually in several previous studies.[4 5 19 20]

The concept of force development was attractive for several reasons. First, it did not require any assumptions regarding ventricular geometry or size. Second, it did not need measurement of ventricular volumes. Third, it was not affected by variation in heart rate over the physiological range encountered. Fourth, it represented an estimation of the energy transferred from right and left ventricular myocardial shortening to work done by accelerating blood into the pulmonary and systemic circulations respectively.

The cross sectional areas of the pulmonary artery were consistently greater than those of the aorta throughout the period of gestation studied, but the reverse was true of the peak blood flow velocities. The mean stroke volume ejected by the right ventricle was more than 20% greater than that ejected by the left ventricle for the population as a whole; this result accorded with previous reports.[4 5] Acceleration time was longer in the aorta than in the pulmonary artery, as has been previously described,[21] and varied inversely with heart rate. Acceleration time was longer in the aorta, whereas in normal children and adults acceleration time in the pulmonary artery is longer, as is the right ventricular ejection time.

The main finding in this study was that the force developed by the right and left ventricles was similar throughout the latter part of the second and third trimesters even though the right ventricle ejected a significantly greater stroke volume than did the left ventricle. The myocardial force in both ventricles increased more than tenfold from 20 weeks to term and this increase paralleled the increase in heart weight and total body weight,[3 22] indicating that force increases as myocardial mass increases with fetal growth. The variability in force development in the third trimester most probably relates to the variability in fetal body habitus and therefore myocardial mass.

The similarity between the force developed by the two ventricles was initially surprising in view of the significantly different stroke volumes. Myocardial systolic shortening in the intact ventricle is determined by several factors, important among which are ventricular chamber geometry and ventricular loading conditions or afterloads.[23 24] Calculation of right and left ventricular afterloads requires the measurement of chamber diameters, wall thicknesses, and ventricular systolic pressures. Left and right ventricular diameters, wall thicknesses, and free wall weights were found to be similar in the human fetus when they were measured in vivo by ultrasound and in vitro in necropsy specimens,[3 22] indicating similar right and left ventricular chamber geometry. However, right and left ventricular systolic pressures cannot be measured in the human fetus and therefore ventricular afterloads cannot be quantified. In the fetal lamb, which has been used extensively as an experimental model, right and left ventricular systolic pressures are equal,[25 26] and there is little reason to believe they are different in the human fetus. Thus ventricular afterload, which is the force that the myocardium must overcome to eject blood into the pulmonary or systemic circulations, must be the same in the two ventricles. Because afterload varies inversely with ventricular fractional shortening further evidence that right and left ventricular afterloads are equivalent is provided by the observation that fractional shortening is similar in the right and left ventricles. Since right and left ventricular chamber geometries, afterloads, and myocardial shortening are all closely similar, it is easier to understand how the two ventricles develop the same amount of myocardial force even though their respective volume handling is different. The right ventricle ejects a larger stroke volume than the left ventricle, but does so at a lower velocity than the left ventricle.

We describe a non-invasive method of assessing right and left ventricular performance in terms of myocardial force in the human fetus. The study showed that the force developed by the right and left ventricles is similar and increases more than tenfold from 20 weeks to term. We submit that this quantitative method of assessing ventricular function may be of clinical value not only in the normal fetus but also in monitoring fetuses with impaired ventricular function.

1 Sahn DJ, Lange LW, Allen HD, Goldberg SJ, Anderson C, Giles J, *et al.* Quantitative real-time cross-sectional echocardiography in the developing normal human fetus and newborn. *Circulation* 1980,62:588–97.
2 Allan LD, Joseph MC, Boyd EGCA, Campbell S, Tynan M. M-mode echocardiography in the developing human fetus *Br Heart J* 1982,47:573–83.
3 St John Sutton M, Gewitz MH, Shah B, Cohen A, Reichek R, Gabbe S, *et al.* Quantitative assessment of growth and function of the cardiac chamber in the normal human fetus a prospective longitudinal study *Circulation* 1984,69:645–54.
4 Reed KL, Meijboom EJ, Sahn DJ, Scagnelli SA, Valdes-Cruz L M, Shenker L Cardiac Doppler flow velocities in human fetuses. *Circulation* 1986;73·41–6
5 Kenny JF, Plappert T, Doubilet P, Saltzman DH, Cartier M, Zollars L, *et al.* Changes in intracardiac blood flow velocities and right and left ventricular stroke volumes with gestational age in the normal human fetus: a prospective Doppler echocardiographic study. *Circulation* 1986;74:1208–16.
6 Anderson PAW, Glick KL, Killam AP, Mainwaring RD. The effect of heart rate in utero on left ventricular output in the fetal sheep. *J Physiol (Lond)* 1986,372:557–73.
7 Kenny J, Plappert T, Doubilet P, Saltzman D, St John Sutton M. Effects of heart rate on ventricular size, stroke volume, and output in the normal human fetus; a prospective Doppler echocardiographic study. *Circulation* 1987,76:52–8
8 Kleinman CS, Donnerstein RL, Devore GR, Jaffe CC, Lynch DC, Berkowitz RL, *et al.* Fetal echocardiography for evaluation of in utero congestive heart failure. *N Engl J Med* 1982;306:568–75
9 Katz VL, Seeds JW. Fetal and neonatal cardiovascular complications from B-sympathomimetic therapy for tocolysis. *Am J Obstet Gynecol* 1989,161:1–4
10 Gill RW. Measurement of blood flow by ultrasound: accuracy and sources of error *Ultrasound Med Biol* 1985,11:625–41.
11 Griffin D, Cohen-Overbeek T, Campbell S. Fetal Utero-placental blood flow. *Clin Obstet Gynecol* 1983;10·565–74.
12 Campbell S, Newman GB. Growth of the fetal biparietal diameter during normal pregnancy. *J Obstet Gynecol Br Commonwealth* 1971;73 513–9.
13 Kurtz AB, Warner RJ, Dershaw DD, Rubin CS, Cole-Beuglet C, Goldberg BB. Analysis of biparietal diameters as an accurate indicator of gestational age. *J Clin Ultrasound* 1980,8.319–26.
14 Isaaz K, Ethevenot G, Admant P, Brembilla B, Pernot C. A new Doppler method of assessing left ventricular ejection force in chronic congestive heart failure. *Am J Cardiol* 1989,64:81–7.
15 St John Sutton M, Theard M, Bhatia SJS, Plappert T, Doubilet P, Saltzman DH Changes in placental blood flow in the normal human fetus with gestational age *Pediatr Res* 1990,28:383–8.
16 Friedman WF The intrinsic physiologic properties of the developing heart. *Prog Cardiovasc Dis* 1972;15:87–111.
17 Carey RA, Bove AA, Coulson RL, Spann JF. Correlation between cardiac muscle myosin ATP'ase activity and velocity of muscle shortening. *Biochem Med* 1979;21·235–45.
18 Schwartz K, Le Carpentier Y, Martin JL, Lompre AM, Mercadier JJ, Swynghedauw B. Myosin isoenzyme distribution correlates with speed of myocardial contraction *J Mol Cell Cardiol* 1981;13 1074–5.
19 Angelini A, Allan LD, Anderson RH, Crawford DC, Chita SK, Ho SY. Measurements of the dimensions of the aortic and pulmonary pathways in the human fetus: a correlative echocardiographic and morphometric study *Br Heart J* 1988;60·221–6.
20 Cartier MS, Davidoff A, Warneke LA, Hirsch MP, Bannon S, St John Sutton M, *et al.* The normal diameter of the fetal aorta and pulmonary artery. Echocardiographic evaluation in utero. *AJR* 1987;149 1003–7.
21 Machado MVL, Chita SC, Allan LD Acceleration time in the aorta and pulmonary artery measured by Doppler echocardiography in the midtrimester normal human fetus. *Br Heart J* 1987;58:15–8.
22 St John Sutton M, Raichlen JS, Reichek N, Huff DS Quantitative assessment of right and left ventricular growth in the human fetal heart: a pathological study. *Circulation* 1984;70:935–41.
23 Weber KT, Janicki JS The dynamics of ventricular contraction, force, length and shortening *Fed Proc* 1980,39 188–95.
24 Borow KM, Green LH, Grossman W, Braunwald E. Left ventricular end-systolic stress shortening and stress-length relationships in humans. normal values and sensitivity to inotropic state. *Am J Cardiol* 1982;50 1301–8.
25 Rudolph AM. Organization and control of the fetal circulation In. Jones C, Nathaniels PW, eds· *The physiological development of the fetus and newborn* London: Academic Press, 1985 343–53.
26 Rudolph AM, Heymann MA. Fetal and neonatal circulation and respiration. *Annu Rev Physiol* 1974;19 187–201

Br Heart J 1991;66:290–4

Non-invasive measurement of the regurgitant fraction by pulsed Doppler echocardiography in isolated pure mitral regurgitation

Christophe Tribouilloy, Wei Feng Shen, Michel A Slama, Hervé Dufossé,
Dominique Choquet, Alain Marek, Jean-Philippe Lesbre

Abstract

***Objective*—To assess the usefulness of pulsed Doppler echocardiography as a method of measuring the regurgitant fraction in patients with mitral regurgitation.**

***Patients and methods*—Twenty controls and 27 patients with isolated mitral regurgitation underwent Doppler studies. In the patients the study was performed within 48 hours of cardiac catheterisation. Aortic outflow was measured in the centre of the aortic annulus, and mitral inflow was derived from the flow velocity at the tip of the leaflets and the area of the elliptical mitral opening. The regurgitant fraction was calculated as the difference between the two flows divided by the mitral inflow.**

***Results*—In the 20 controls the two flows were almost identical (mitral inflow, 4·44 (SD 0·88) l/min; aortic outflow, 4·58 (SD 0·84) l/min), with a mean regurgitant fraction of 4·2 (SD 8·4)%. In patients with mitral regurgitation, the mitral inflow was significantly higher than the aortic outflow (8·8 (3·6) *v* 4·3 (1·1) l/min). In most patients the Doppler-derived regurgitant fraction (45·8 (19·2)%) accorded closely with the regurgitant fraction (41·3 (SD 17·8)%) determined by the haemodynamic technique.**

***Conclusion*—Pulsed Doppler echocardiography, with an instantaneous velocity-valve area method for calculating mitral inflow, reliably measured the severity of regurgitation in patients with mitral regurgitation.**

Both flow mapping of regurgitant jets by pulsed Doppler echocardiography and planimetry of jet area by Doppler colour flow imaging in the left atrium during ventricular systole have been used to evaluate the degree of mitral regurgitation.[1 2] These approaches, however, give semiquantitative rather than actual volumetric assessments of regurgitation.[3] Recent studies have examined the validity of pulsed Doppler method for measuring the regurgitant fraction based on the aortic and mitral flows.[4-6] Despite satisfactory correlations between Doppler and haemodynamic results, the accuracy and reliability of measuring regurgitation remain uncertain, because mean flow velocity and mitral valve area are used to determine mitral inflow. We used an instantaneous velocity-valve area method to measure mitral inflow, and we compared the Doppler-derived regurgitant fraction with that obtained by a combined haemodynamic-angiographic method.

Department of Cardiology, South Hospital, University of Picardie, Amiens, France
C Tribouilloy
W F Shen
M A Slama
H Dufossé
D Choquet
A Marek
J-P Lesbre

Correspondence to Professor Jean-Philippe Lesbre, Service de Cardiologie B, Hôpital Sud, 80000 Amiens cedex, France.

Accepted for publication 8 May 1991

Patients and methods

PATIENTS

We studied 31 patients who had echocardiographic examination and cardiac catheterisation. Four patients were excluded because of poor echogenicity and the remaining 27 patients formed the study population. There were 13 men and 14 women with mean age of 57 (SD 17, range 29–81) years. All had angiographically documented isolated and pure mitral regurgitation. The cause of mitral regurgitation was mitral prolapse in 14, rheumatic fever in two, endocarditis in two, rupture of chordae tendineae in five, and dilated cardiomyopathy in four. Twenty four patients were in sinus rhythm and three in atrial fibrillation.

Valvar regurgitation was excluded by clinical and Doppler echocardiographic examinations in 20 controls (15 men and 5 women, mean age 35 (SD 11, range 24–42) years. All were in sinus rhythm.

ECHOCARDIOGRAPHY

The ultrasound examination was performed with a Hewlett-Packard (mode 77020 A) Doppler imaging system. A 2·5 MHz transducer was used for M mode, cross sectional, and pulsed Doppler examinations. The filter was set at 400 Hz. All measurements and calculations were done by an observer without knowledge of haemodynamic data.

Aortic outflow measurement

The diameter of the aortic annulus was determined in the left parasternal long axis view just proximal to the point of insertion of the aortic cusps during midsystole. The aortic surface area was calculated by assuming a circular geometry. The aortic flow velocity was measured by pulsed Doppler method in the apical five chamber view, placing the sample volume at the level of the aortic annulus. The time-velocity integral, a product of mean velocity and ejection time, was calculated by directly tracing the area under the instantaneous velocity curve on the screen. The aortic outflow was derived as the product of aortic surface area times velocity integral and heart rate.[7] In our laboratory, a previous study of 22 patients without valvar regurgitation showed that aortic outflow determined by pulsed Doppler method was almost identical with cardiac output measured by thermodilution technique.[8]

Mitral inflow measurement

The mitral inflow was determined on the assumption that the mitral orifice was ellipsoid.[9] The long axis of the mitral orifice (equivalent to the diameter of the mitral annulus) was assessed at the insertion of the mitral leaflets during middiastole in the apical four chamber view and was assumed to be constant during diastole. The short axis of the mitral orifice, which changed with time, was measured by digitising the innermost contour of representative mitral valve leaflets on M mode echocardiograms recorded in left parasternal long axis or short axis views with a paper speed of 100 mm/s. The instantaneous mitral valve area was equal to $(\pi/4) \times L \times S(t)$, where L is the mitral long axis and S (t) the mitral short axis. The mitral flow velocity was measured by pulsed Doppler method under cross sectional guidance in an apical four chamber view; the sample volume was positioned just at the tip of the mitral leaflets (fig 1). The angle of incidence between mitral flow vector and ultrasound beam was always placed as close to zero as possible to avoid underestimation of the peak flow velocity. A representative mitral Doppler velocity curve with fully delineated mitral envelope (with clear opening and closing points) was selected to measure instantaneous mitral flow velocity. Heart rate during M mode and Doppler measurements was identical. The mitral stroke volume was calculated as the product of the instantaneous valve area and instantaneous velocity. The mitral inflow was the product of the instantaneous mitral stroke volume and heart rate. We have already shown by an instantaneous velocity-valve area method that the pulsed Doppler-derived mitral inflow was almost identical to aortic outflow in 30 patients without valvar regurgitation.[10]

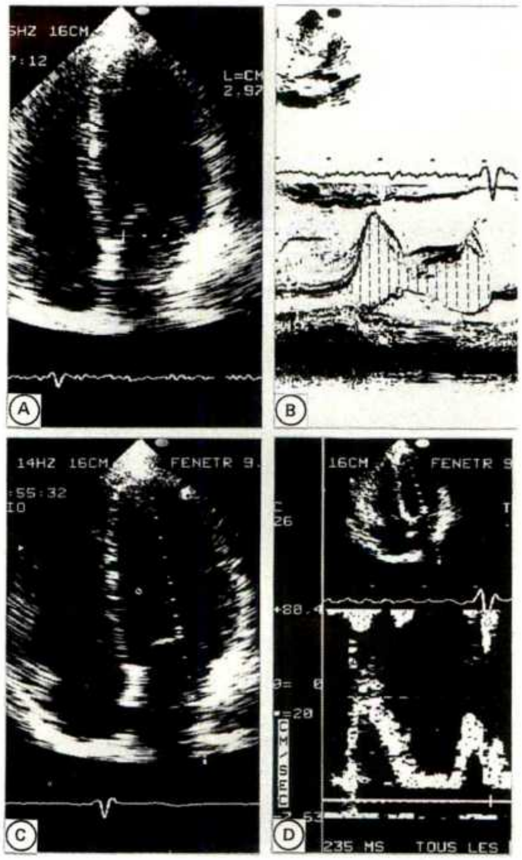


Figure 1 Determination of mitral inflow by an instantaneous velocity-valve area method. The diameter of the mitral annulus (L) in the apical four chamber view was used as the long axis of the mitral valve (A). The short axis of the mitral orifice was measured by digitising the innermost contour of representative mitral valve leaflets on M mode echocardiogram (B). The instantaneous mitral valve area was derived from constant long axis (L) and varying short axis (S(t)), assuming that the area was ellipsoid. The mitral flow velocity curve recorded at the tip of the mitral leaflets was digitised to measure instantaneous velocity (C and D). The mitral stroke volume was the product of the instantaneous valve area and instantaneous velocity. The mitral inflow was calculated as the product of mitral stroke volume and heart rate.

The regurgitant fraction was derived from a standard formula: regurgitant fraction = [(mitral inflow − aortic outflow)/mitral inflow] × 100.

CARDIAC CATHETERISATION

Right and left heart catherisations were performed within 48 hours of Doppler studies in all patients with mitral regurgitation. Forward cardiac output was measured by the thermodilution technique using the average of five consecutive measurements. Left ventriculography was performed in 30° right anterior oblique projection, and left ventricular end diastolic and end systolic volumes were measured by the single plane area-length method. A 1 cm grid was filmed for correction of magnification, and the Kennedy regression equation was used to correct the overestimation of ventricular volumes. The angiographic left ventricular output (containing forward and regurgitant volumes) was calculated as the product of left ventricular stroke volume and heart rate. The heart rate was determined as an average of 10 cardiac cycles during atrial fibrillation. The regurgitant fraction was calculated as the difference between angiographic and thermodilution output divided by angiographic output and expressed as percentage.

The angiographic severity of mitral regurgitation was graded according to the method of Sellers *et al*.[11]

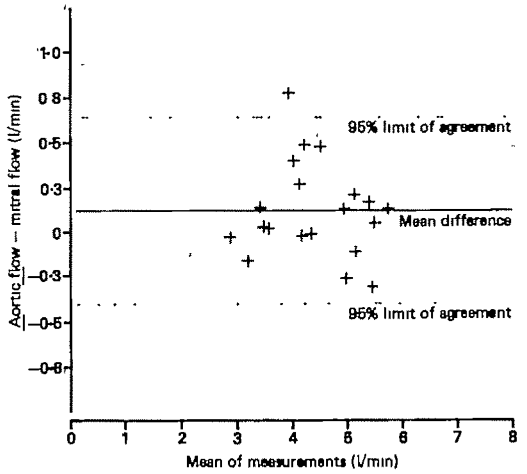
REPRODUCIBILITY STUDIES

We assessed the reproducibility of the method by analysing data from ten patients with coronary artery disease who were studied serially in our laboratory. These patients were selected because they did not have mitral or aortic regurgitation and because they had had two Doppler studies at an interval of two months. Both studies were performed by the same technician and the regurgitant fraction was determined as the difference between mitral and aortic flows divided by mitral flow. Reproducibility studies after a two month interval in patients with mitral regurgitation could not be performed because it could not be determined whether an observer change was real or induced by the errors of the method.

STATISTICAL ANALYSIS

Data are expressed as mean (SD). We assessed the agreement between mitral inflow and aortic outflow in normal subjects and between Doppler and haemodynamic regurgitant fraction in patients with mitral regurgitation by the method of Bland and Altman.[12]

Figure 2 Difference between Doppler measurements of aortic outflow and mitral inflow plotted against the mean value in 20 controls.



Results

CONTROLS

There was a close agreement between the mitral inflow and the aortic outflow. The 95% limits of agreement were +0·68 to −0·42 l/min (fig 2). The mean mitral inflow and aortic outflow were 4·44 (SD 0·88, range 2·99–5·78) and 4·58 (SD 0·84, range 2·96–5·91) l/min, respectively. The difference between the two flows was <0·6 l/min in 19 (95%) of the 20 controls. The mean regurgitant fraction was 4·2 (8·4)%, with a regurgitant fraction of <10% in 19 (95%).

PATIENTS WITH MITRAL REGURGITATION

The table summarises the clinical, haemodynamic, and Doppler findings. There was good agreement between the Doppler and haemodynamic regurgitant fractions (fig 3). The 95% limits of agreement were −10 to +19%. The mitral inflow was significantly greater than the aortic outflow by both techniques. The regurgitant fraction varied from 11·1 to 73·3% by the Doppler method and from 8·8 to 67·0% by the haemodynamic method. The mean value of the regurgitant fraction measured by Doppler (45·8 (19·2)%) was significantly higher than that measured haemodynamically (41·3 (17·8)%) ($p < 0.01$). However, in 24 (89%) out of 27 patients, the difference in regurgitant fraction between the two methods was <11%. All patients with an estimated regurgitant fraction of 50% by Doppler had an angiographic grade of III or IV. The Doppler-derived regurgitant fraction was closely related to the grade of regurgitation estimated by left ventriculography (fig 4).

REPRODUCIBILITY

The mean regurgitant fraction obtained in the 10 patients with coronary artery disease during the two serial examinations was 6·9 (4·5)% and 6·8 (2·7)%. For each patient, the difference between the two regurgitant fractions was ≤10%.

Discussion

MEASUREMENT OF REGURGITANT FRACTION IN MITRAL REGURGITATION

By assessing systolic flow disturbance in the left atrium, pulsed Doppler echocardiography has been used to detect accurately the presence of mitral regurgitation and to provide a semiquantitative evaluation of its severity.[1] Several studies have reported the usefulness of the Doppler method in measuring the regurgitant fraction in isolated mitral regurgitation by estimating flow volume across the mitral orifice during diastole and through aortic orifice during systole.[4 6] Blumlein *et al* calculated total left ventricular output from cross sectional dimensional echocardiographic volume determinations and measured forward flow from the product of M mode derived aortic valve area and the flow velocity integral in the ascending

Clinical, haemodynamic, and Doppler echocardiographic features in 27 patients with mitral regurgitation

				Doppler determination			Haemodynamic determination			
	Age (yr)	Sex	Rhythm	Aortic flow (l/min)	Mitral flow (l/min)	RF (%)	Forward output (l/min)	Total LV output (l/min)	RF (%)	Grade
1	51	M	Sinus	7·1	10·9	34·9	6·6	8·9	25·8	II
2	29	F	Sinus	4·0	4·7	14·9	5·3	5·9	10·2	I
3	58	F	Sinus	2·2	5·0	56·0	2·4	4·8	50·0	III
4	63	M	Sinus	3·3	6·2	46·8	5·0	12·1	58·7	III
5	71	F	AF	3·2	9·0	64·4	3·8	8·6	55·8	III
6	53	M	Sinus	4·5	13·7	67·2	5·8	13·3	56·4	III
7	30	F	Sinus	5·1	10·9	53·2	8·0	12·6	36·5	III
8	59	F	Sinus	2·7	6·6	59·1	4·4	8·9	50·6	III
9	53	F	Sinus	5·1	8·7	41·4	7·9	9·8	19·4	III
10	59	F	AF	4·0	13·2	69·7	4·6	11·6	60·3	III
11	19	F	Sinus	5·1	13·6	62·5	6·5	15·9	59·1	IV
12	64	F	Sinus	3·6	10·4	65·4	3·8	11·5	67·0	IV
13	66	F	Sinus	4·4	10·6	58·5	4·7	10·7	56·1	IV
14	55	M	Sinus	5·4	10·0	46·0	5·7	10·9	47·7	III
15	55	M	Sinus	5·0	7·1	29·6	4·5	6·2	27·4	II
16	76	M	Sinus	3·4	5·8	41·4	5·5	8·5	35·3	II
17	67	M	Sinus	5·0	8·0	37·5	4·4	7·5	41·3	II
18	80	M	Sinus	3·9	8·5	54·1	3·9	7·0	44·3	IV
19	69	F	AF	3·9	7·2	45·8	2·2	3·8	42·1	III
20	17	M	Sinus	4·5	5·3	15·1	4·2	5·5	23·6	I
21	68	F	Sinus	3·1	4·1	24·4	3·2	3·9	17·9	II
22	49	M	Sinus	4·6	5·2	11·5	5·2	5·7	8·8	I
23	81	F	Sinus	3·2	9·4	66·0	2·5	5·7	56·1	IV
24	50	M	Sinus	4·0	4·5	11·1	4·2	4·8	12·5	I
25	76	F	Sinus	4·0	5·5	27·3	4·7	7·1	33·8	II
26	51	M	Sinus	4·0	15·0	73·3	4·6	12·2	62·3	IV
27	38	F	Sinus	7·1	18·0	60·6	9·0	18·0	50·0	IV

AF, atrial fibrillation; LV, left ventricular; RF, regurgitant fraction.

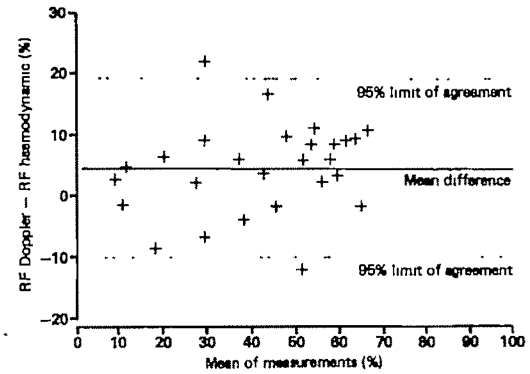


Figure 3 Difference between Doppler and haemodynamic measurements of regurgitant fraction (RF) plotted against the mean value.

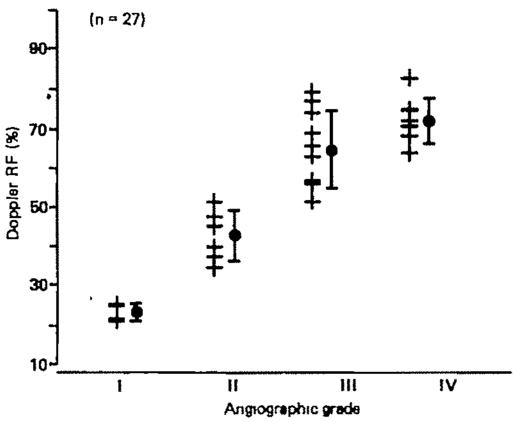


Figure 4 Relation between the Doppler-derived regurgitant fraction (RF) and the angiographic grade of mitral regurgitation. The correlation coefficient for linear regression is 0 92 (p < 0 001). Mean (SD) of Doppler measurements is plotted for each angiographic grade.

aorta assessed by continuous wave Doppler analysis.[6] Because the assessment of left ventricular volumes by cross sectional echocardiography depends largely upon a geometric assumption of the left ventricle, the regurgitant fraction derived from this method may not be accurate and this limits its clinical usefulness. Other groups used the pulsed Doppler technique to estimate the regurgitant fraction by measuring both the aortic and mitral flows.[4 5 13] In these studies, though the aortic outflow was measured by a similar method to ours, the assessment of the mitral inflow differed. Rokey *et al* used the mitral annulus as the sampling site for both Doppler recording of mitral inflow velocity and cross sectional mitral diameter, and based the calculation of the mitral inflow on a circular mitral orifice.[4] Zhang *et al*[5] measured velocities at the tip of the mitral leaflets and derived a mean mitral valve area by the method previously developed by Fisher *et al* in animal experiments.[14] However, previous studies of diastolic flow pattern and mitral dynamics showed that both the mitral orifice area and flow velocity change during diastole.[15 16] It is, therefore, necessary to correct for such variations when mitral inflow is determined. We[10] and others[9 17] showed that the left ventricular inflow was overestimated if the mitral annulus was assumed to be circular and underestimated when a single (mean) value was used to calculate the diastolic mitral orifice area. Because the regurgitant fraction was derived from the difference between mitral inflow and aortic outflow divided by mitral inflow, an accurate determination of the mitral inflow is crucial and an error in estimation of regurgitant fraction may be exaggerated from small errors in the stroke volume determination across the mitral valve.[5]

The instantaneous velocity-valve area method that we used integrates the mitral flow velocity and orifice at each instant of diastole, on the assumption that only the long axis of the mitral valve orifice is temporally and spatially constant. The correlation between Doppler and haemodynamic mitral flow measurements was considerably improved when this approach was used for a wide range of stroke volume and cardiac output estimates.[9] In our study the instantaneous velocity-valve area method gave almost identical mitral inflow and aortic outflow in the controls. In patients with isolated mitral regurgitation, the regurgitant fraction calculated by this method agreed closely with both the qualitative and quantitative assessments of severity of mitral regurgitation by the haemodynamic method.

POTENTIAL LIMITATIONS OF DOPPER METHOD

Considerable errors can arise from calculations of volume flow by Doppler techniques, particularly when the valve area is estimated and where two volumes need to be measured at different sites. We found some differences between the mitral inflow and the aortic outflow measured by the pulsed Doppler method in the controls when the mean regurgitant fraction was 4·2 (8·4)%. There was an overlap between the regurgitant fraction measurements in the controls and the patients with mild mitral regurgitation—one control had a regurgitant fraction of $>11\%$. This highlights an important limitation of the technique and indicates that meticulous care is necessary to ensure the quality of information being obtained. Our study differs from previous reports in which a 15% regurgitant fraction was often seen in the control group.[4] Furthermore, a similar falsely high regurgitant fraction was reported in controls assessed by the haemodynamic method.[18] In patients with mitral regurgitation, the mean value of the regurgitant fraction measured by the Doppler method was slightly but significantly greater than when the regurgitant fraction was determined haemodynamically. Nevertheless, the present study showed a good agreement between Doppler measurement of regurgitant fraction and haemodynamic assessment of the severity of mitral regurgitation, indicating that both techniques could differentiate accurately the various grades of regurgitation in patients with mitral regurgitation.

In patients with atrial fibrillation, considerable variations in diastolic time can make estimation of the regurgitant fraction less accurate because of the impossibility of simultaneously recording Doppler and M mode echocardiograms. Assessment of the regurgitant fraction is reasonably accurate if the measurement is derived from the average of several carefully time-matched cardiac cycles, though this is tedious and time-consuming.

The Doppler method of measuring regurgitation in patients with mitral regurgitation in this study may not be reliable when mitral stenosis is present and the mitral valve orifice is distorted. In this condition the long axis of the mitral valve is not equivalent to the diameter of the mitral annulus. The mitral valve area may be calculated from the pressure half-time of diastolic velocity or could be directly measured on cross sectional echocardiograms.[19 20] In patients with mixed mitral and aortic regurgitation, the severity of mitral regurgitation may be underestimated by the method because the aortic outflow is overestimated. In these patients, an accurate measure of mitral regurgitation may be obtained by measuring pulmonary flow as effective forward output and mitral inflow as total flow.[21]

We found that an instantaneous velocity-valve area method for calculating mitral inflow gave a reliable and accurate measure of the regurgitant fraction in isolated mitral regurgitation. Despite its limitations, the method may be useful in assessing the severity of valve disease and evaluating the effects of therapeutic interventions in patients with isolated mitral regurgitation.

---

1 Abbasi AS, Allen MW, De Cristofaro D, Ungar I. Detection and estimation of the degree of mitral regurgitation by rang-gated pulsed Doppler echocardiography. *Circulation* 1979,61·143–7.

2 Spain MG, Smith MD, Grayburn PA, Harlamert EA, De Maria AN. Quantitative assessment of mitral regurgitation by Doppler color flow imaging. angiographic and haemodynamic correlations *J Am Coll Cardiol* 1989, 13·585–90

3 Shah PM. Quantitative assessment of mitral regurgitation *J Am Coll Cardiol* 1989,13:591–3

4 Rokey R, Sterling LL, Zoghbi WA, *et al* Determination of regurgitant fraction in isolated mitral and aortic regurgitation by pulsed Doppler two-dimensional echocardiography. *J Am Coll Cardiol* 1986;7 1273–8.

5 Zhang Y, Ihlen H, Myhre E, Levorstad K, Nitter-Hauge S Measurement of mitral regurgitation by Doppler echocardiography *Br Heart J* 1985,54.384–91

6 Blumlein S, Bouchard A, Schiller NB, *et al.* Quantitation of mitral regurgitation by Doppler echocardiography *Circulation* 1986;14·306–14.

7 Lewis JF, Kuo L, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output clinical validation of two methods using the apical window *Circulation* 1984,10:425–31

8 Dericbourg C, Tribouilloy C, Kugener H, Avinée P, Rey JL, Lesbre JP Mesure non invasive du débit cardiaque par echocardiographie Doppler pulsé corrélation avec la thermodilution *Arch Mal Coeur* 1990;83:237–44

9 De Zuttere D, Touche T, Saumon G, Nitenberg A, Prasquier R. Doppler echocardiographic measurement of mitral flow volume· validation of a new method in adult patients. *J Am Coll Cardiol* 1988;11.343–50

10 Tribouilloy C, Slama MA, Shen WF, *et al.* Determination of left ventricular inflow by pulsed Doppler echocardiography. influence of mitral orifice area and blood velocity measurements. *Eur Heart J* 1991,12 39–43

11 Sellers RD, Levy MJ, Amplatz K, Lillehei CW Left retrograde cardioangiography in acquired cardiac disease. *Am J Cardiol* 1964;14.437–42

12 Bland JM, Altman DG Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986,i.307–10.

13 Ascah KJ, Stewart WJ, Jiang L, *et al.* A Doppler-two-dimensional echocardiographic method for quantitation of mitral regurgitation *Circulation* 1985,72.377–83

14 Fisher DC, Sahn DJ, Firedman MJ, Larson DJ, Allen HD. The mitral valve orifice method for noninvasive two-dimensional echo-Doppler determinations of cardiac output *Circulation* 1983,67 872–8

15 Taylor DEM, Whamond JS Velocity profile and impedance of the healthy mitral valve. In Kalmanson D, ed. *The mitral valve. A pluridisciplinary approach.* London Edward Arnold, 1976:127–36.

16 Ormiston JA, Shah PM, Tei C, Wong M. Size and motion of the mitral valve annulus in man I. A two-dimensional echocardiographic method and findings in normal subjects. *Circulation* 1981,64:113–20

17 Dittman H, Voelker W, Karsch KR, Seipel L Influence of sampling site and flow area on cardiac output measurements by Doppler echocardiography. *J Am Coll Cardiol* 1987,10 818–23.

18 Lopez JF, Hanson S, Orchard RC, Tan L Quantification of mitral valvular incompetence *Cathet Cardiovasc Diagn* 1985,11:139–52.

19 Martin RP, Rakowski H, Kleiman JH, Beaver W, London E, Popp RL Reliability and reproducibility of two-dimensional echocardiographic measurement of the stenotic mitral valve orifice area. *Am J Cardiol* 1979,43 560–5

20 Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. *Circulation* 1979;60 1096–8

21 Kitabatake A, Ito H, Inone M, *et al* A new approach to noninvasive evaluation of aortic regurgitant fraction by two-dimensional Doppler echocardiography. *Circulation* 1985;72.523–9.

Br Heart J 1991;66:295–301

Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease

Peter H Groves, Neil P Lewis, Shahid Ikram, René Maire, Roger J C Hall

Department of Cardiology, University Hospital of Wales, Cardiff
P H Groves
N P Lewis
S Ikram
R Maire
R J C Hall

Correspondence to
Dr Peter H Groves,
Department of Cardiology,
University Hospital of
Wales, Heath Park, Cardiff
CF4 4XW

Accepted for publication
8 May 1991

Abstract

***Objective*—To determine how severe tricuspid regurgitation influences exercise capacity and functional state in patients who have undergone successful mitral valve replacement for rheumatic mitral valve disease.**

***Design*—9 patients in whom clinically significant tricuspid regurgitation developed late after mitral valve replacement were compared with 9 patients with no clinical evidence of tricuspid regurgitation. The two groups were matched for preoperative clinical and haemodynamic variables. Patients were assessed by conventional echocardiography, Doppler echocardiography, and a maximal treadmill exercise test in which expired gas was monitored by mass spectrometry.**

***Setting*—University Hospital of Wales, Cardiff.**

***Subjects*—18 patients who had been reviewed regularly since mitral valve replacement.**

***Main outcome measure*—Objective indices of exercise performance including exercise duration, maximal oxygen consumption, anaerobic threshold, and ventilatory response to exercise.**

***Results*—Mitral valve prosthetic function was normal in all patients and estimated pulmonary artery systolic pressure and left ventricular function were similar in the two groups. Right ventricular diameter (median (range) 5·0 (4·3–5·6) *v* 3·7 (3·0–5·4) cm, $p < 0{\cdot}01$) and the incidence of paradoxical septal motion (9/9 *v* 3/9, $p < 0{\cdot}01$) were greater in the group with severe tricuspid regurgitation. Exercise performance—assessed by exercise duration (6·3 (5·0–10·7) *v* 12·7 (7·2–16·0) min, $p < 0{\cdot}01$), maximum oxygen consumption (11·2 (7·3–17·8) *v* 17·7 (11·8–21·4) ml min^{-1} kg^{-1}, $p < 0{\cdot}01$), and anaerobic threshold (8·3 (4·6–11·4) *v* 0·7 (7·3–15·5) ml min^{-1} kg^{-1}, $p < 0{\cdot}05$)—was significantly reduced in the group with severe tricuspid regurgitation. The ventilatory response to exercise was greater in patients with tricuspid regurgitation (minute ventilation at the same minute carbon dioxide production (41·0 (29·9–59·5) *v* 33·6 (26·8–39·3) l/min, $p < 0{\cdot}01$).**

***Conclusions*—Clinically significant tricuspid regurgitation may develop late after successful mitral valve replacement and in the absence of residual pulmonary hypertension, prosthetic dysfunction, or significant left ventricular impairment. Patients in whom severe tricuspid regurgitation developed had a considerable reduction in exercise capacity caused by an impaired cardiac output response to exercise and therefore experienced a poor functional outcome. The extent to which this was attributable to the tricuspid regurgitation itself or alternatively to the consequences of right ventricular dysfunction was not clear and requires further investigation.**

Successful mitral valve replacement for rheumatic mitral valve disease is accompanied in most patients by a sustained symptomatic improvement.[1-3] Continuation or return of limiting symptoms may indicate the presence of prosthetic valve failure, impairment of left ventricular function, persistent pulmonary hypertension, or the development of important aortic valve disease. All may lead to a rise in right heart pressures and the subsequent development of functional tricuspid regurgitation. We found that severe tricuspid regurgitation can develop in the absence of these factors and that it can also be responsible for a poor functional outcome. Attention has been paid in the past to the importance of right ventricular function as a determinant of exercise capacity in heart failure.[4 5] In chronic left ventricular failure, exercise capacity seems to correlate with resting right ventricular ejection fraction[5] and pulmonary vascular resistance.[6] Although not previously studied, the presence of severe tricuspid regurgitation is likely to be associated with a reduced right ventricular output and would also be expected to compromise exercise capacity in the absence of left ventricular impairment.

Clinical assessment was a poor guide to true functional state after valve replacement[7] and the criteria applied are by their nature subjective with poor interobserver reproducibility.[8] Exercise testing, incorporating expired gas analysis, is now well established as a safe, reliable, and reproducible method of studying the pathophysiological response to exercise in patients with heart failure.[9 10] It is also valuable as a method of assessing accurately the severity of cardiac disease and correlating this with the extent of functional limitation.[11 12]

The aim of this study was to establish by exercise testing with expired gas analysis how the presence of severe tricuspid regurgitation influenced exercise capacity and functional state in patients who had undergone successful mitral valve replacement for rheumatic mitral valve disease.

Patients and methods

Eighteen patients were studied; nine (eight women, one man) had developed clinically significant tricuspid regurgitation late after successful mitral valve replacement for rheumatic mitral valve disease. Their mean age was 59 years (range 48–67). All patients had experienced an initial symptomatic improvement after operation but they described the return of limiting symptoms when clinical signs of tricuspid regurgitation became apparent. Clinically significant tricuspid regurgitation was diagnosed in the presence of a raised jugular venous pressure with prominent cv wave, pulsatile hepatomegaly, and fluid retention requiring intensive diuretic treatment. Nine patients (eight women, one man) who had also undergone mitral valve replacement for rheumatic mitral valve disease were chosen as a closely matched control group. Their mean age was 62 years (range 56–67). When we selected these patients we attempted to match clinical, preoperative haemodynamic, operative, and current echocardiographic indices as closely as possible (tables 1 and 2). None had clinical signs of tricuspid regurgitation or a history of postoperative fluid retention. All patients in both groups were in atrial fibrillation.

Patients were questioned about current cardiac symptoms, and functional capacity was assessed according to the New York Heart Association (NYHA) classification. During clinical examination we noted the presence or absence of physical signs suggesting tricuspid regurgitation. The jugular venous pressure was examined with the patient sitting at 45°. The mean of the venous waveforms was estimated clinically and the height measured in centimetres above the sternal angle. This value was used to derive an indirect measurement of right atrial pressure. Results of preoperative cardiac catheterisation and the details of valve surgery were obtained from the patient records.

ECHOCARDIOGRAPHY

Standard transthoracic echocardiography was performed with a Hewlett Packard 77510A scanner in all patients. Cross sectional, M mode, and Doppler echocardiography with continuous wave, pulsed wave, and colour flow Doppler were performed in all standard views. The examination was performed with all subjects in the left lateral decubitus and supine positions. M mode echocardiograms were recorded at a paper speed of 100 mm/s. Variables derived from the M mode echocardiogram and Doppler recordings were measured for five consecutive beats and a mean value was calculated.

The left ventricular dimensions were recorded in the long axis view as the greatest dimensions of the left ventricle obtained at the level of the mitral valve prosthesis. The minor axis dimensions were measured between the endocardial surfaces of the posterior wall and interventricular septum. The end diastolic dimension (EDD) was taken at the peak of the R wave of the simultaneously recorded electrocardiogram. The end systolic dimension (ESD) was defined as the minimum distance separating the endocardial surfaces at the peak upward anterior motion of the posterior ventricular wall. Fractional shortening was calculated by the following formula:

$$\mathrm{FS}\,(\%) = \frac{\mathrm{LVEDD} - \mathrm{LVESD}}{\mathrm{LVEDD}} \times 100$$

The right ventricular end diastolic dimension was measured as the distance between the endocardial surfaces of the right ventricle at the R wave of the simultaneously recorded electrocardiogram. The direction of septal motion in early systole was recorded and judged to be either normal or paradoxical.

Prosthetic valve function was studied by visual inspection of the cross sectional echocardiogram and by Doppler assessment. Continuous wave Doppler signals of diastolic mitral flow velocity were recorded and an estimate of mitral valve area was derived from the pressure half time. Mitral regurgitation was sought by pulsed wave echocardiography and colour flow Doppler mapping in apical and left parasternal views.

Tricuspid regurgitation was detected in all 18 subjects and was apparent with both continuous wave and colour flow Doppler. Doppler recordings of maximal velocity were obtained from the apical and left parasternal views and continuous wave Doppler signals were considered optimal once the maximum clearly defined spectral envelope was achieved. The peak velocity (v) of the tricuspid regurgitation jet was used to calculate the systolic tricuspid valve gradient from a modified Bernoulli equation:

$$\text{TV gradient (mm Hg)} = 4\,v^2$$

The systolic pressure gradient across the tricuspid valve represents the difference between the right ventricular and right atrial systolic pressures. The right ventricular systolic pressure (and also pulmonary artery systolic pressure) can therefore be estimated if the pressure gradient and right atrial pressure are known.[13] Right atrial pressure was estimated by adding 5 cm to the mean clinical jugular venous pressure assessment[14] and converted to mm Hg by dividing the right atrial pressure in centimetres by 1·3 to take account of the relative densities of mercury and blood at physiological temperatures.[15]

The severity of tricuspid regurgitation was estimated echocardiographically and graded as mild, moderate, or severe. This semiquantitative assessment was made on the basis of the width of the regurgitant jet and the distance to which it extended into the right atrium, as detected by colour flow and pulsed wave Doppler. Tricuspid regurgitation was graded as mild if the regurgitant jet was narrow and extended into the right atrium no further than one third the length of the inter-atrial septum and severe if the jet was broad, reached the posterior atrial wall, and was detected in the hepatic vein. Intermediate findings were judged to reflect moderate tricuspid regurgitation.

EXERCISE TESTING

Symptom limited maximal exercise testing was performed according to the Weber treadmill protocol,[9] which is a progressive exercise protocol designed for heart failure patients. Subjects continued their normal medication on the day of exercise testing. The heart rate and electrocardiogram were recorded continuously and a standard 12 lead electrocardiogram was performed every minute. Blood pressure was recorded by mercury sphygmomanometer every two minutes. Respiratory gas analysis was performed during exercise by mass spectrometry (Airspec 2000, Biggin Hill, UK) by means of the argon dilution technique.[16] Minute oxygen consumption ($\dot{V}O_2$, ml min^{-1} kg^{-1}), minute carbon dioxide production ($\dot{V}CO_2$, ml min^{-1} kg^{-1}), and minute ventilation ($\dot{V}E$, l/min) were measured every 15 seconds. Exercise duration and maximal oxygen consumption (defined as the mean oxygen consumption during the final 30 seconds of exercise) were recorded. The anaerobic threshold was determined by computerised analysis of a curve fitting model of the relation between oxygen consumption and carbon dioxide production.[17] The ventilatory response to exercise was determined from linear regression analysis of the relation between minute ventilation and carbon dioxide production.[18 19]

ANALYSIS OF RESULTS

All data are reported as medians and ranges. Results obtained for the two groups were compared by a Mann-Whitney test for continuous variables and a Fisher exact probability test for non-continuous variables. A p value of $<0·05$ was regarded as statistically significant.

Results

CLINICAL

Table 1 summarises clinical details of the two groups. They were well matched for age, sex, and duration of symptoms before operation and were studied at similar intervals postoperatively. All patients were in atrial fibrillation and none had significant coronary artery disease or aortic valve disease. The preoperative haemodynamic findings were similar in the two groups, as were the type and size of mitral valve prostheses implanted (table 1). None of the patients with clinically significant tricuspid regurgitation had an abnormal right atrial 'v' wave at preoperative cardiac catheterisation, while one patient in the control group had a right atrial 'v' wave up to 12 mm Hg. Mild tricuspid regurgitation was detected by palpation at operation in four of those who subsequently developed clinically significant tricuspid regurgitation but was absent in all patients in the control group.

ECHOCARDIOGRAPHY

Table 2 summarises the echocardiographic findings. All the indices of left ventricular function were similar in the two groups. None of the patients in either group had evidence of prosthetic valve dysfunction and none had developed significant aortic valve disease. The estimated pulmonary artery systolic pressure was not significantly higher in patients with severe tricuspid regurgitation, but the right ventricular diameter and the incidence of paradoxical septal motion were significantly greater ($p < 0·01$) in this group.

The tricuspid valve was found to be thickened in six patients with clinically significant tricuspid regurgitation and in eight patients in the control group. Tricuspid valve motion, however, remained free in all those studied and none had cross sectional echocardiographic features that suggested valve stenosis or valve prolapse. The degree of tricuspid regurgitation was judged to be severe in six patients and moderate in three of the patients with clinically significant tricuspid regurgitation. In contrast, regurgitation was found to be moderate in five patients and mild in four patients in the control group.

Table 1 Clinical, preoperative cardiac catheterisation, and surgical details of the two patient groups (median (range))

	TR (*n* = 9)	*Control* (*n* = 9)	*p*
Age (yr)	60·0 (53 5–67 7)	62 8 (56 2–67 4)	NS
Sex (F/M)	8/1	8/1	—
Symptom duration preoperatively (yr)	2 (1–11)	2 (2–6 5)	NS
Time after operation (yr)	10 2 (2 8–17 8)	6 3 (3·5–11 8)	NS
NYHA class III + IV preoperatively	7	5	—
NYHA class III + IV currently	9	0	—
Dominant mitral valve lesion:			
Stenosis	7	7	—
Regurgitation	2	2	—
Pulmonary artery systolic pressure (mm Hg)	35 (25–90)	35 (16–105)	NS
Good left ventricular contraction	9	9	—
Organic tricuspid valve disease	0	0	—
Prosthesis:			
Disc	6	5	
Ball and cage	1	1	—
Tissue	2	3	
Prosthetic size (mm)	27 (25–31)	29 (25–31)	NS

TR, tricuspid regurgitation.

Table 2 Echocardiographic results (median (range))

Variable	*TR* *(n = 9)*	*Control* *(n = 9)*	*p*
LVEDD (cm)	5·1 (2·3–7·9)	4·3 (3·7–5·5)	NS
LVESD (cm)	3·8 (1·3–6·4)	3·2 (2·6–4·5)	NS
FS (%)	23 (16–33)	24 (17–39)	NS
RV diameter (cm)	5·0 (4·3–5·6)	3·7 (3·0–5·4)	<0·01
Paradoxical septal motion	9	3	<0·01
Pulmonary artery systolic pressure (mm Hg)	33 (31–53)	27 (16–67)	NS
MV area (cm²)	2·7 (1·8–3·4)	1·9 (1·2–4·2)	NS

FS, fractional shortening; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; MV, mitral valve; RV, right ventricle, TR, tricuspid regurgitation.

Table 3 Ventilatory changes and indices of performance during exercise (median (range))

Variable	*TR* *(n = 9)*	*Control* *(n = 9)*	*p*
Exercise duration (min)	6·3 (5·0–10·7)	12·7 (7·2–16·0)	<0·01
RER:			
Rest	0·86 (0·72–0·88)	0·81 (0·74–0·88)	NS
Maximum	1·03 (0·93–1·06)	1·06 (0·95–1·22)	NS
$\dot{V}_E/\dot{V}CO_2$ slope	37·9 (28·5–57·5)	30·8 (22·9–33·4)	<0·01
Minute ventilation at CO_2 production of 1 l/min (l/min)	41·0 (29·9–59·5)	33·6 (26·8–39·3)	<0·01
Maximum increase in SBP (mm Hg)	8·0 (−18–30)	22·0 (2–50)	<0·05
Maximum increase in HR (min^{-1})	40 (11–73)	74 (20–77)	0·05
$\dot{V}O_2$ max (ml min^{-1} kg^{-1})	11·2 (7·3–17·8)	17·7 (11·8–21·4)	<0·01
Anaerobic threshold (ml min^{-1} kg^{-1})	8·3 (4·6–11·4)	10·7 (7·3–15·5)	<0·05

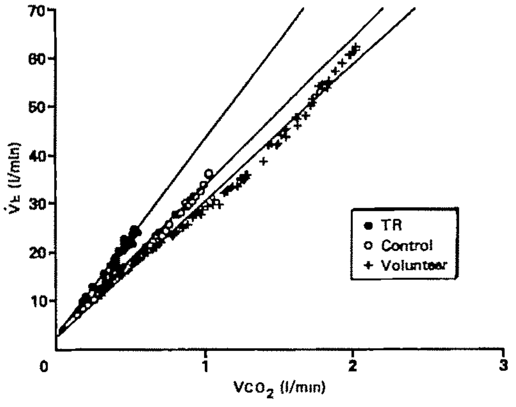
HR, heart rate, RER, respiratory exchange ratio (CO_2 produced: O_2 consumed); SBP, systolic blood pressure; $\dot{V}_E/\dot{V}CO_2$ slope is derived by linear regression and expresses the relation between ventilation ($\dot{V}_E$) and carbon dioxide production ($\dot{V}CO_2$) during exercise; $\dot{V}O_2$ max, maximum oxygen consumption.

EXERCISE TESTING

Resting respiratory exchange ratio was normal in all patients and increased during exercise (table 3). The mean respiratory exchange ratio at peak exercise in both groups exceeded 1·0, indicating maximal exercise and the onset of anaerobic metabolism, with production of lactate and therefore a rise in carbon dioxide production relative to the amount of oxygen consumed. An exaggerated hyperpnoeic response to exercise was seen in patients with clinically significant tricuspid regurgitation but not in the control group. The linear relation between minute ventilation and carbon dioxide production (total ventilatory response) was significantly steeper (figure), so that minute ventilation was increased relative to the same carbon dioxide production (table 3). Patients with tricuspid regurgitation had a blunted haemodynamic response to exercise with significantly smaller rises in both heart rate and systolic blood pressure (table 3). Exercise duration, maximum oxygen consumption, and anaerobic threshold were significantly lower in patients with tricuspid regurgitation than in the controls (table 3).

Discussion

Our results show that the presence of clinically significant tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease was associated with a considerable impairment of exercise capacity and a poor functional outcome. We were careful to compare the exercise performance of patients with severe tricuspid regurgitation with that of a well matched control group to eliminate other variables that were likely to influence exercise capacity. In particular, we specifically chose patients in both groups with well preserved resting left ventricular function on echocardiography, in order to concentrate on the influence exerted by the right heart on exercise performance. Although this method of left ventricular assessment is relatively crude, our principal object was to minimise differences between the two groups rather than to establish whether or not left ventricular function was normal in all patients. Pulmonary artery systolic pressure was also similar in the two groups and none of the patients had prosthetic dysfunction or important aortic valve disease. We conclude that the substantial differences in exercise capacity seen between the groups could only be explained by the presence or absence of tricuspid regurgitation. An exaggerated hyperpnoeic response to exercise[19] and



Relation between minute ventilation and carbon dioxide production during exercise for representative (median) patients from the two groups studied and a healthy volunteer.

reductions in maximal oxygen consumption[9,20] and anaerobic threshold[20,21] reflect an impaired overall cardiac output response to exercise in patients with heart failure. This is also presumably the mechanism by which exercise capacity is reduced in patients with tricuspid regurgitation—that is, by limiting the increase in right ventricular cardiac output that can be achieved during exercise. Our findings, however, do not enable us to determine whether this is because of a progressively failing right ventricle, of which tricuspid regurgitation is merely a marker, or whether a large tricuspid regurgitant fraction is itself primarily responsible for a reduction in forward flow. In either case, our results corroborate evidence suggesting that events in the right heart are important in determining exercise capacity.[4-6]

It is not clear why significant tricuspid regurgitation developed in these patients. Echocardiography showed thickening of the tricuspid valve in two thirds of the patients with clinically significant tricuspid regurgitation; but this was also a common finding among those in the control group and was never accompanied by abnormal cusp motion. Thickening of the tricuspid valve is a non-specific finding at echocardiography and the cross sectional echocardiogram is generally able to identify when it is accompanied by valve stenosis and is a feature of organic rheumatic tricuspid valve disease.[22] In the absence, therefore, of organic tricuspid valve disease, we assume that tricuspid regurgitation is functional in these patients. Neither significant pulmonary arterial nor venous hypertension were present and it is likely, therefore, that severe functional tricuspid regurgitation develops either as a result of progressive right ventricular dysfunction or as a result of persistent dilatation of the tricuspid valve annulus. Because we studied these patients when the consequences of severe tricuspid regurgitation were likely to be advanced, it is difficult to determine which is most likely. Right ventricular dysfunction could develop as a result of tricuspid regurgitation but the reverse is also true. This difficult question has important therapeutic implications. Surgical correction of tricuspid regurgitation may be of some benefit if persistent annular dilatation is the dominant underlying abnormality, while it may be no help or even detrimental if annular dilatation is secondary to right ventricular dysfunction.

King *et al* retrospectively analysed their results of surgery for tricuspid regurgitation that developed late after mitral valve replacement.[23] Of 32 patients, 14 had no evidence of prosthetic valve dysfunction or significant aortic valve disease; however, they did not comment on indices of left ventricular function or pulmonary artery systolic pressure in these patients. Tricuspid valve replacement was performed in 11 patients while three underwent tricuspid valve annuloplasty. Only four patients, however, improved by at least one NYHA class, while three patients died in the early postoperative period because of a low cardiac output and six died during the following six years. One patient remained in NYHA class IV. They concluded that tricuspid regurgitation developing late after mitral valve replacement in their patients was a manifestation of right ventricular failure and that restoring tricuspid valve competence was of little benefit. Though their results are certainly disappointing, we cannot conclude that tricuspid valve surgery has no part in the management of this heterogeneous group. It may be, for example, that patients with a relatively low pulmonary artery systolic pressure and well preserved left ventricular function would experience better results from tricuspid valve repair or replacement. Certainly, before dismissing the role of surgery, it would be necessary prospectively to study the benefits of correcting tricuspid regurgitation, both on functional state and on outcome, in patients with severe tricuspid regurgitation but without pulmonary hypertension, left ventricular dysfunction, or prosthetic valve failure.

Of perhaps more importance, given the apparent high mortality of reoperation on the tricuspid valve[23] and the considerable functional limitation that we showed in these patients, is that much is to be gained in attempting to reduce the likelihood of severe tricuspid regurgitation developing after mitral valve replacement. This may best be achieved by the accurate detection and correction of important tricuspid regurgitation at initial surgery. Tricuspid regurgitation is a common finding in patients with advanced mitral stenosis or regurgitation and may be present in more than 50% of those requiring mitral valve replacement.[24,25] Traditional methods of assessment both preoperatively and at the time of surgery are imprecise.[26] Haemodynamic measurements are of limited value in assessing the severity of tricuspid regurgitation[24,26,27] and digital examination of the amount of tricuspid regurgitation present at operation is influenced by many variables which make it unreliable.[28] These methods of pre and per operative assessment were used in our group of patients and it is possible that the degree of tricuspid regurgitation was underestimated. Czer *et al* suggest that intraoperative colour flow mapping is a more reliable and reproducible method of assessing the severity of tricuspid regurgitation and of selecting patients who need surgical repair of the tricuspid valve.[26] They report a favourable comparison between this technique and right ventricular angiography, which has previously been regarded as the "gold standard" but which is rarely performed. Intraoperative colour flow mapping can certainly be performed easily and may be of benefit both in assessing the severity of tricuspid regurgitation and also in judging the adequacy of tricuspid valve repair.

Although accurate assessment of tricuspid regurgitation is now possible, its subsequent surgical management remains controversial. Braunwald *et al* originally suggested that non-organic tricuspid regurgitation would regress after adequate correction of left sided lesions,[29] but it is now recognised that this is often not the case.[26,30,31] Failure to correct significant tricuspid regurgitation at the time of surgery may be an important factor that leads to subsequent progressive right heart failure and worsening tricuspid regurgitation. There is much debate, however, about the best method of preventing this. Tricuspid valve replacement is usually reserved for those with either very severe tricuspid regurgitation or organic tricuspid valve disease with accompanying stenosis.[30 32] In those without organic tricuspid valve disease or with less severe tricuspid regurgitation, annuloplasty may be performed. Deloche *et al* established that in functional tricuspid regurgitation five sixths of the annular dilatation occurs at the base of the anterior and posterior leaflets, with only one sixth occurring at the insertion of the septal leaflet.[33] Kay *et al*[34] described a method of annuloplasty of the tricuspid valve involving plication of the posterior leaflet, producing a bicuspid valve but eliminating only 50% of the annular dilatation.[35] This was accompanied by high and unpredictable failure rates.[30 35] The method of De Vega,[36] however, leads to a uniform plication of the anterior and posterior leaflets because circumferential sutures are placed around the annulus; this results in a semicircular deformation of the tricuspid orifice. Alternatively, insertion of a prosthetic valve ring was described by Carpentier *et al*,[37] with the shape of the ring conforming to that of the tricuspid valve and producing a predictable correction with a normal valve orifice and usually excellent valve function. Rivera *et al* compared the use of De Vega annuloplasty and the Carpentier ring and found better results with the Carpentier ring.[38] The Carpentier ring procedure produced a better anatomical repair[28] and by the use of interrupted sutures distributed the holding force over the entire ring, producing a more effective and durable reduction in tricuspid regurgitation.[26] Whichever approach is adopted it seems that the long term prognosis is often poor.[28 29] McGrath *et al* report that among 530 patients undergoing a tricuspid valve procedure during surgery for valvar heart disease, 14·7% died in hospital, while 40% of those who survived the original procedure died during late follow up.[39] The presence of significant tricuspid regurgitation usually indicates advanced valve disease and it is possible that earlier surgery would reduce the necessity for intervention at the tricuspid valve and improve the overall long term results of surgery.

In conclusion, we showed that patients who develop significant tricuspid regurgitation late after successful mitral valve replacement for rheumatic mitral valve disease have a considerable reduction in exercise capacity resulting in a poor functional outcome. Exercise testing with expired gas analysis indicates that this is attributable to an impaired cardiac output response to exercise resulting from failure of the right ventricle or from the influence that tricuspid regurgitation itself has in limiting a rise in right ventricular cardiac output. Residual pulmonary hypertension was not present and left ventricular function was well preserved in these patients. Given the relatively high risk of re-operation involving the tricuspid valve and the degree of functional limitation shown in these patients, efforts should be made to reduce the likelihood of severe tricuspid regurgitation developing after mitral valve replacement. This may best be achieved by the accurate intraoperative detection and correction of important tricuspid regurgitation at the time of initial surgery. If surgery were considered at an earlier stage of valve disease functional tricuspid regurgitation might become less of a problem.

1 Cohn LH, Allred EN, Cohn LA, *et al* Early and late risk of mitral valve replacement. A 12 year concomitant comparison of the porcine bioprosthetic and prosthetic disc mitral valves. *J Thorac Cardiovasc Surg* 1985,90·872-80
2 Sethia B, Turner MA, Lewis S, *et al*. Fourteen years experience with the Bjork-Shiley tilting disc prosthesis *J Thorac Cardiovasc Surg* 1986;91:350-61.
3 Bloomfield P, Kitchin AH, Wheatley DJ, Walbaum PR, Lutz W, Miller HC A prospective evaluation of the Björk-Shiley, Hancock and Carpentier-Edwards heart valve prostheses. *Circulation* 1986;73:1213-22.
4 Engler R, Ray R, Higgins CB, *et al*. Clinical assessment and follow up of functional capacity in patients with chronic congestive cardiomyopathy *Am J Cardiol* 1982;49. 1832-7.
5 Baker BJ, Wilen MM, Boyd CM, Dinh H, Franciosa JA Relation of right ventricular ejection fraction to exercise capacity in chronic left ventricular failure. *Am J Cardiol* 1984;54 596-9.
6 Franciosa JA, Baker BJ, Seth L. Pulmonary versus systemic haemodynamics in determining exercise capacity of patients with chronic left ventricular failure. *Am Heart J* 1985;110.807-13.
7 Gilmour DG, Spiro SG, Raphael MJ, Freedman S. Exercise tests before and after heart valve replacement. *Br J Dis Chest* 1979;70·185-94
8 Goldman L, Hasmoto B, Cook F, Lascalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class *Circulation* 1981;64.1227-34
9 Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982;65:1213-23.
10 Wilson JR, Ferraro N Exercise intolerance in patients with chronic left heart failure relation to oxygen transport and ventilatory abnormalities. *Am J Cardiol* 1983,51:1358-63.
11 Lipkin DP, Perrins J, Poole-Wilson PA. Respiratory gas exchange in the assessment of patients with impaired ventricular function. *Br Heart J* 1985,54:321-8
12 Franciosa JA. Exercise testing in chronic congestive heart failure. *Am J Cardiol* 1984,53·1447-50.
13 Yock PG, Popp RL. Non-invasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984,70:657-62
14 Braunwald E, ed. *Heart disease · a textbook of cardiovascular medicine*. Philadelphia WB Saunders, 1988 19.
15 Currie PJ, Seward JB, Chan K-L, *et al* Continuous wave Doppler determination of right ventricular pressure. a simultaneous Doppler-catheterisation study in 127 patients *J Am Coll Cardiol* 1985;4:750-6
16 Davies N, Denison DM. Measurement of metabolic gas exchange and minute volume by mass spectrometry alone *Respir Physiol* 1979,36:261-7.
17 Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange *J Appl Physiol* 1986,60·2020-7
18 Lewis NP, Fox KAA, Henderson AH In congestive heart failure (CHF) exercise air spectroscopy provides a sensitive marker for functional status [abstract] *Eur Heart J* 1989,10 438.
19 Buller NP, Poole-Wilson PA Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. *Br Heart J* 1990;63:281-3.
20 Weber KT, Wilson JR, Janicki JS, Likoff MJ Exercise testing in the evaluation of the patient with chronic cardiac failure. *Annu Rev Respir Dis* 1984,129 (suppl 5):60-2.
21 Opasich C, Cobell F, Riccardi G, *et al*. Does the study of anaerobic metabolism give quantitative information on left ventricular dysfunction during exercise. *Eur Heart J* 1988,9 (suppl F) 17-21.
22 Hall RJC, Julian DG *Diseases of the cardiac valves*. New York. Churchill Livingstone, 1989·249.
23 King MR, Schaff HV, Danielson GK, *et al*. Surgery for tricuspid regurgitation late after mitral valve replacement. *Circulation* 1984;70 (suppl I):I-193-7
24 Cohen ST, Sell JE, McIntosh CL, Clark RE. Tricuspid regurgitation in patients with chronic, pure mitral regurgitation. II. Non-operative management, tricuspid valve annuloplasty and tricuspid valve replacement *J Thorac Cardiovasc Surg* 1987,94·488-97
25 Goldman ME, Guarino T, Fuster V, Mindich B. The

necessity for tricuspid valve repair can be determined by intra-operative 2D echocardiography. *J Thorac Cardiovasc Surg* 1987;**94**:542-50.

26 Czer LSC, Maurer G, Bolger A, *et al*. Tricuspid valve repair. Operative and follow-up evaluation by Doppler colour flow mapping. *J Thorac Cardiovasc Surg* 1989;**98**:101-11.

27 Cairnes KB, Klostor FE, Bristow JD, *et al*. Problems in the haemodynamic diagnosis of tricuspid insufficiency. *Am Heart J* 1968;**75**:173-9.

28 Mullany CJ, Gersh BJ, Orszulak TA, *et al*. Repair of tricuspid valve insufficiency in patients undergoing double (aortic and mitral) valve replacement. Perioperative mortality and long term (1 to 20 years) follow-up in 109 patients. *J Thorac Cardiovasc Surg* 1987;**94**:740-8.

29 Braunwald NS, Ross J Jr, Morrow AG. Conservative management of tricuspid regurgitation in patients undergoing mitral valve replacement. *Circulation* 1967;**35** (Pt 2):163-9.

30 Pluth JR, Ellis FH Jr. Tricuspid insufficiency in patients undergoing mitral valve replacement: conservative management, annuloplasty, or replacement. *J Thorac Cardiovasc Surg* 1969;**58**:484-9.

31 Duran CMG, Pomar JL, Colman T, *et al*. Is tricuspid valve repair necessary? *J Thorac Cardiovasc Surg* 1980;**80**:849–59.

32 Breyer RH, McClenathan JH, Michaelis LL, McIntosh CL, Morrow AG. Tricuspid regurgitation: a comparison of non-operative management, tricuspid annuloplasty and tricuspid valve replacement. *J Thorac Cardiovasc Surg* 1976;**72**:862-70.

33 Deloche A, Guerinon J, Fabiani JN, *et al*. Etude anatomique des valvulplasties rhumatismales tricuspidiennes. Application à l'ètude critique des diffèrentes méthodes d'annuloplastie. *Ann Chir Thorac Cardiovasc* 1973;**12**:343-9.

34 Kay JH, Maselli-Campagna G, Tsiyi HK. Surgical treatment of tricuspid insufficiency. *Ann Surg* 1965;**162**:53-8.

35 Grondin P, Meere C, Limet R, *et al*. Carpentier's annulus and De Vega's annuloplasty. *J Thorac Cardiovasc Surg* 1975;**70**:852-9.

36 De Vega NG. La annuloplastia selectiva regulabe y permanente: una tècnicia original para el tratamiento de la insuficienci tricuspide. *Rev Esp Cardiol* 1972;**25**:555–6.

37 Carpentier A, Deloche A, Dauptain J, *et al*. A new reconstructive operation for correction of mitral and tricuspid insufficiency. *J Thorac Cardiovasc Surg* 1971;**61**:1-13.

38 Rivera R, Duran E, Ajuria M. Carpentier's flexible ring versus De Vega's annuloplasty. A prospective randomized study. *J Thorac Cardiovasc Surg* 1985;**89**:196–202.

39 McGrath LB, Gonzalez-Lavin L, Bailey BM, *et al*. Tricuspid valve operations in 530 patients. Twenty-five year assessment of early and late phase events. *J Thorac Cardiovasc Surg* 1990;**99**:124–33.

PLANTS IN CARDIOLOGY

Cinchona ledgeriana Moens ex Trimen. Bentley R, Trimen H. *Medicinal plants*. Vol 2. London: Churchill, 1880:141.

Quinine and quinidine

The bark of the South American tree *Cinchona* (Rubiaceae) contains quinine, and also quinidine—isolated by Pasteur in 1853. Its use in treating fevers was learnt in Peru by Spanish missionaries who in 1630 brought the bark to Europe where its value in malaria was discovered. In 1749 Jean-Baptiste de Sénac wrote "Long and rebellious palpitations have ceded to this febrifuge". In the nineteenth century quinine was used to augment digitalis therapy, and quinidine was described as "das opium des herzens". But the definitive use of quinidine in arrhythmias came about only because of an astute observation in 1912 by a patient of Professor Karel F Wenckebach who then related the story in the *Journal of the American Medical Association* (1923;**81**:472–4). The patient was a man with attacks of atrial fibrillation who said that "being a Dutch merchant used to good order in his affairs he would like to have good order in his heart business also and asked why there were heart specialists if they could not abolish this very disagreeable phenomenon . . . he knew himself how to get rid of his attacks and as I did not believe him he promised to come back next morning with a regular pulse, and he did".

The man had found by chance that when he took one gram of quinine during an attack it reliably halted it in 25 minutes: otherwise it would last for 2–14 days. Quinine was used then not only in malaria but also as a non-specific remedy for minor ailments as aspirin is today. Wenckebach often tried quinine again but he succeeded in only one other patient. However, it led W Frey in Berlin to study all four cinchona alkaloids in atrial fibrillation and in 1918 he showed that quinidine was the most effective. In 1920 Thomas Lewis put forward his famous hypothesis of circus movement and proposed that quinidine restored normal rhythm by closing the gap between the crest and wake of the circus wave.

The family Rubiaceae is huge with over 10 000 species worldwide. Emetine comes from ipecacuanha and caffeine from coffee but there are no other medicinal species. One genus has the splendid name of *Captaincookia*. Quinine and quinidine are still obtained naturally, from the species *Cinchona ledgeriana* grown commercially in the tropics.

A HOLLMAN

Br Heart J 1991;66:302–7

Role of transoesophageal echocardiography in evaluation of cardiogenic embolism

I W Black, A P Hopkins, L C L Lee, B M Jacobson, W F Walsh

Abstract

Objective—**To determine the value of transoesophageal echocardiography in the assessment of selected patients at risk of cardiogenic embolism or after it.**

Design—**Prospective comparison of the results of transoesophageal and transthoracic echocardiography. Transoesophageal echocardiography was performed with a 5 MHz single plane phased array transducer.**

Setting—**University teaching hospital.**

Patients—**100 patients referred for transoesophageal echocardiography after a cerebral ischaemic event or peripheral arterial embolism (n = 63), before percutaneous balloon dilatation of the mitral valve (n = 23), or before electrical cardioversion of atrial fibrillation (n = 14).**

Results—**Transthoracic echocardiography showed potential sources of embolism in four patients including left ventricular thrombus in two patients (with one false positive), left atrial appendage thrombus (n = 1), and patent foramen ovale (n = 1). Transoesophageal echocardiography showed 59 potential embolic sources in 45 patients including left atrial spontaneous echo contrast (n = 33), left atrial appendage thrombus (n = 13), left ventricular thrombus (n = 5), patent foramen ovale (n = 3), left ventricular spontaneous echo contrast (n = 2), mitral valve prosthesis thrombus (n = 1), mitral valve prolapse (n = 1), and pronounced aortic atheroma (n = 1). Transoesophagal echocardiography showed potential embolic sources in 36/53 (68%) patients with atrial fibrillation compared with 9/47 (19%) patients in sinus rhythm. Percutaneous balloon dilatation of the mitral valve was performed without embolic complications in 18 patients without left atrial thrombi and in three patients with small fixed thrombi in the left atrial appendage. It was cancelled in two patients with large thrombi in the left atrial appendage. Cardioversion was performed without embolic complications in 14 patients without left atrial thrombi.**

Conclusions—**Transoesophageal echocardiography detects potential sources of embolism better than transthoracic echocardiography in selected patients at risk of cardiogenic embolism or after it.**

Department of Cardiovascular Medicine, Prince Henry/Prince of Wales Hospitals, Sydney, Australia
I W Black
A P Hopkins
L C L Lee
B M Jacobson
W F Walsh

Correspondence to
Dr W F Walsh, Department of Cardiovascular Medicine, Prince Henry Hospital, Anzac Parade, Little Bay, Sydney 2036, Australia

Accepted for publication
29 April 1991

Cardiogenic embolism accounts for 15% of ischaemic strokes and transient ischaemic attacks[1 2] and is an important cause of systemic arterial embolism.[3] Cardiogenic embolism can also complicate therapeutic procedures, including percutaneous balloon dilatation of the mitral valve[4] and cardioversion of atrial fibrillation.[5]

Transthoracic echocardiography has been used to detect intracardiac thrombi and other potential cardiac sources of embolism.[6 7] Recently the use of transoesophageal echocardiography to detect left atrial thrombi and other cardiac sources of embolism has been reported.[8–11] This technique provides high quality imaging of the cardiac anatomy including the left atrial body and appendage, which are close to the oesophagus, without interference from the chest wall and lungs.[12]

In a preliminary report in patients with a history of embolism, transoesophageal echocardiography was found to be more sensitive than transthoracic echocardiography for the detection of left atrial thrombi and also of left atrial spontaneous echo contrast.[10] The latter term refers to swirling, smoke-like echoes seen in the left atrial cavity in patients with relative stasis of left atrial blood,[13] and this feature was reported to be an independent predictor of thromboembolic risk in patients with mitral valve disease.[14] Furthermore, there is little information about the role of transoesophageal echocardiography in patients undergoing procedures with a risk of cardiogenic embolism, such as electrical cardioversion of atrial fibrillation and percutaneous balloon dilatation of the mitral valve.

We prospectively assessed the overall role of transoesophageal echocardiography in the detection of potential cardiac sources of embolism by comparing the results of transoesophageal with those of transthoracic echocardiography both in patients referred after suspected cardiogenic embolism and in patients before procedures with a risk of cardiogenic embolism.

Patients and methods

PATIENTS

Between October 1988 and April 1990, 100 patients (62 women and 38 men, mean age 60 (range 25–86)) were referred for transoesophageal echocardiography after suspected cardiogenic embolism (n = 63), before percutaneous balloon dilatation of the mitral valve (n = 23), or before DC cardioversion of atrial fibrillation (n = 14).

Sixty three patients were referred for the detection of potential cardiac sources of emboli after a cerebral ischaemic event or acute peripheral arterial occlusion. Patients were selected for transoesophageal echocardiography if cardiogenic embolism was clinically suspected and if transthoracic echocardiography alone was considered unlikely to detect potential embolic sources. Studies were performed within one month of the event in 59/63 (94%) patients. Fifty two patients were studied after stroke or transient ischaemic attack. Cerebral infarction was shown by computed tomography or magnetic resonance imaging in 35/52 (67%) patients. The remaining 11 patients were studied after acute thromboembolism to the arm or leg, documented at surgery in 10/11 patients. Two patients referred after suspected embolism had mitral stenosis and six patients had a mitral valve prosthesis.

Twenty three patients were studied before elective percutaneous balloon dilatation of the mitral valve. Transoesophageal echocardiography was routinely performed one day before dilatation to assess mitral valve anatomy and function and to detect left atrial thrombi.

Fourteen patients were referred to exclude left atrial thrombus before elective DC cardioversion of atrial fibrillation. Atrial fibrillation had lasted less than one month in seven patients and more than one month in seven patients.

Transoesophageal echocardiography was unsuccessful in two additional patients, referred after stroke, who were excluded from further analysis. Oesophageal intubation was unsuccessful in one patient and the second patient was unable to tolerate the endoscope despite apparently adequate sedation.

Twenty one of the 100 patients also underwent 26 follow up studies; 16 studies to assess the mitral valve apparatus and to detect possible iatrogenic atrial septal defects after percutaneous balloon dilatation of the mitral valve, and 10 studies to assess the effect of anticoagulant therapy on cardiac thrombi. One patient refused follow up study.

METHODS

All patients had initial conventional cross sectional and Doppler transthoracic echocardiography, including colour flow mapping, with 1·9 MHz, 2·5 MHz, and 3·5 MHz transducers (Hewlett Packard 77020A). Mitral valve area was calculated by the Doppler pressure half-time method.[15]

Transoesophageal echocardiography was performed with a standard 5 MHz single plane phased array transducer (Hewlett Packard 21236A). Written informed consent was obtained and the patients were examined in the fasting state. Intravenous sedation (midazolam with fentanyl) was given in 93/126 (74%) of studies. Previously described tomographic planes,[12] including basal short axis, four chamber, transgastric short axis, and views of the thoracic aorta were obtained. Particular attention was directed to the left atrial body and appendage and the interatrial septum. The left ventricular endocardium was examined in sequential transgastric short axis views as well as in four-chamber views.

Intracardiac thrombus was diagnosed by the presence of a clearly defined echodense intracavitary mass, acoustically distinct from the underlying endocardium and not caused by pectinate ridges of the atrial appendage. Mital valve prolapse was diagnosed by transoesophageal echocardiography according to previously reported criteria.[9] From November 1989, contrast studies to detect a patient foramen ovale were performed during transoesophageal echocardiography in patients in whom no other source of embolism had been found (n = 25). Agitated saline containing air microbubbles was injected rapidly into an antecubital vein and the patient was instructed to perform a Valsalva manoeuvre or to cough.[16] A patent foramen ovale with right to left shunting was diagnosed if microbubbles were seem to cross the atrial septum into the left atrium and no septal defect was seen.

The study period lasted 10–20 minutes and technically adequate images were obtained in all studies. There were no complications. All clinical and echocardiographic data were recorded prospectively. Transoesophageal and transthoracic echocardiographic studies were performed and interpreted independently by different experienced echocardiographers, who were, however, not blinded to the transthoracic echocardiography results.

Differences in proportions were compared by the χ^2 test with continuity correction. Statistical significance was defined as $p < 0{\cdot}05$.

Results

Table 1 summarises echocardiographic findings in the 100 initial studies. Transoesophageal echocardiography was significantly more sensitive than transthoracic echocardiography in the detection of left atrial appendage thrombus ($p < 0{\cdot}005$) and of left atrial spontaneous echo contrast ($p < 0{\cdot}0001$). In the 47 patients in sinus rhythm, transoesophageal echocardiography showed potential embolic sources in nine (19%) patients whereas thoracic echocardiography showed them in three patients (6%) (p = NS). In the 53 patients with atrial fibrillation, transoesophageal echocardiography showed potential embolic sources in 36 patients (68%) and transthoracic echocardiography showed them in one patient (2%) ($p < 0{\cdot}0001$).

Table 1 Echocardiographic findings

	Transthoracic	*Transoesophageal*
Normal	96	55
Left atrial SEC	0	33
Left atrial appendage thrombus	1	13
Left ventricular thrombus	2	5
Patent foramen ovale	1	3
Left ventricular SEC	0	2
Mitral valve prolapse	0	1
Mitral prosthesis thrombus	0	1
Aortic atheroma	0	1

SEC, spontaneous echo contrast.

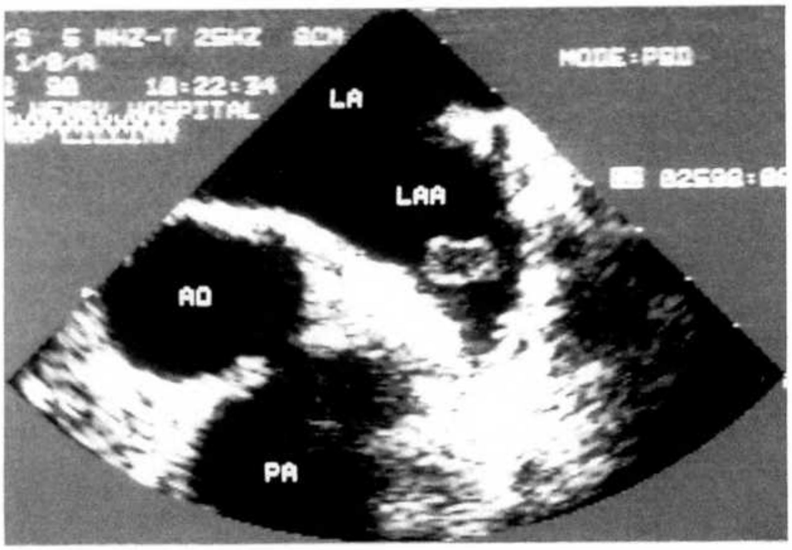


Figure 1 Thrombus in the left atrial appendage of a patient with atrial fibrillation and recent stroke. LA, left atrium; LAA, left atrial appendage; AO, aorta; PA, pulmonary artery.

CEREBRAL AND PERIPHERAL EMBOLISM

Thirty six of the 63 patients were in sinus rhythm and 27 were in atrial fibrillation, including three patients with paroxysmal atrial fibrillation. In the 36 patients who were in sinus rhythm, three (8%) had potential cardiac sources of embolism shown by transthoracic echocardiography. The transthoracic echocardiographic study was interpreted as showing left ventricular thrombus in two patients and patent foramen ovale (shown by colour flow mapping) in one patient. In one of the patients with left ventricular thrombi and a patent foramen ovale the diagnosis was confirmed by transoesophageal echocardiography. The other apparent left ventricular thrombus was shown to be a branching network of false tendons at the left ventricular apex. In the 33 patients with negative transthoracic studies, transoesophageal echocardiography showed potential embolic sources in four patients. Small left ventricular thrombi were found in two patients; one patient was also shown to have both left ventricular spontaneous contrast and a patent foramen ovale. One patient had posterior leaflet mitral valve prolapse not clearly demonstrated by transthoracic echocardiography. One patient with mitral stenosis and left atrial enlargement (M mode dimension 52 mm) was shown to have a left atrial appendage thrombus.

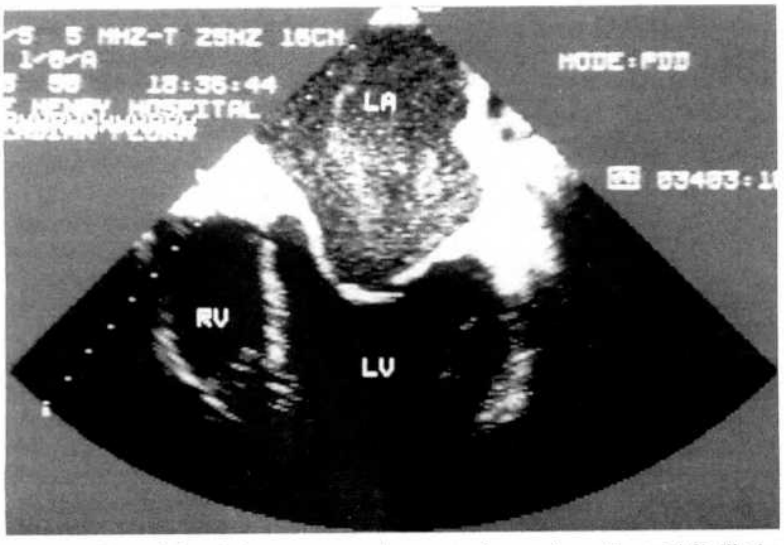


Figure 2 Dense left atrial spontaneous echo contrast in a patient with atrial fibrillation and mitral stenosis. LA, left atrium; LV, left ventricle; RV, right ventricle.

None of the 27 patients with atrial fibrillation had potential embolic sources shown by transthoracic echocardiography compared with 21/27 (78%) patients in whom they were shown by transoesophageal echocardiography. Six patients had a thrombus in the left atrial appendage (fig 1) associated with left atrial spontaneous echo contrast in four patients. Eleven patients had left atrial spontaneous echo contrast without thrombus, including one patient with associated left ventricular spontaneous echo contrast and one with a patent foramen ovale. Two patients had small left ventricular thrombi, one patient without evidence of endocarditis had echoes consistent with thrombus on a mechanical mitral valve prosthesis, and one patient with embolism to the leg had considerable atheroma of the descending thoracic aorta.

Transoesophageal echocardiography showed potential sources of embolism in 22/52 patients with cerebral ischaemic events and in 5/11 patients with acute peripheral arterial occlusion (p = NS). Left atrial thrombi were found in one of two patients with mitral stenosis, one of six patients with mitral valve prostheses, and 5/22 patients with non-valvar atrial fibrillation. All five patients with left ventricular thrombus had previous anterior myocardial infarction. Eleven of the 13 patients found to have cardiac thrombi were receiving anticoagulant therapy at the time of study, and after the finding of left atrial appendage thrombus anticoagulant therapy was started in two patients not previously treated.

Four patients with thrombus at initial transoesophageal echocardiography underwent eight follow up studies after the start of warfarin treatment. Left atrial appendage thrombi were unchanged in two patients studied serially up to nine and 13 months. A left atrial appendage thrombus was found to have resolved in one patient after eight months. A left ventricular thrombus was found to have resolved at five months in one patient.

PERCUTANEOUS BALLOON DILATATION OF THE MITRAL VALVE

Eleven of the 23 patients were in sinus rhythm and 12 were in atrial fibrillation. In the 11 patients in sinus rhythm (mean mitral valve area 1·0 cm^1) neither echocardiographic study showed thrombus while transoesophageal echocardiography alone showed left atrial spontaneous echo contrast in three patients.

In 12 patients with atrial fibrillation (mean mitral valve area 1·2 cm^2) transthoracic echocardiography showed a large left atrial appendage thrombus in only one patient, which was confirmed by transoesophageal echocardiography and subsequent surgery. In the remaining 11 patients, left atrial thrombus was shown by transoesophageal echocardiography in five,

Table 2 *Effect of percutaneous balloon dilatation of the mitral valve on left atrial spontaneous echo contrast (SEC)*

Group	*n (AF)*	*Mitral valve area* *Pre dilatation*	 *Post dilatation*
(I) No SEC in either study	6 (1)	1·3 (1·0–1·9)	1·6 (1·0–2·2)
(II) Persistence of SEC	7 (6)	1·1 (0·9–1·4)	1·5 (1·4–1·9)
(III) Resolution of SEC	3 (1)	0·9 (0·8–1·2)	2·2 (2·0–2·4)

Mitral valve mean area and range are shown. AF, atrial fibrillation.

all in the appendage and all associated with left atrial spontaneous echo contrast. Five patients had left atrial spontaneous echo contrast alone (fig 2). Only one patient had neither thrombus nor spontaneous contrast.

Balloon dilatation of the mitral valve was not performed in three of the six patients with thrombus, all with large thrombi in the atrial appendage. One patient was treated medically and the second patient underwent mitral valve replacement at which the presence of a left atrial appendage thrombus was confirmed. Warfarin was started in the third patient who underwent successful percutaneous balloon dilatation of the mitral valve six months later after repeat transoesophageal echocardiography showed complete resolution of the thrombus. Three other patients had small fixed thrombi at the apex of the left atrial appendage. Percutaneous balloon dilatation of the mitral valve was performed in these patients with the Inoue balloon technique[17] without embolic or other complication. All 18 patients without evidence of left atrial thrombus underwent balloon dilatation without embolic complications.

Sixteen patients had follow up transoesophageal echocardiography three months after valve dilatation. Table 2 shows the effect of valve dilatation on left atrial spontaneous echo contrast. In three patients with left atrial appendage thrombus at initial study, the thrombi had resolved at follow up study in one patient with persistence of spontaneous contrast and in one patient with resolution of spontaneous contrast. One patient with resolution of spontaneous contrast had partial resolution of thrombus.

One patient in chronic atrial fibrillation and little change in mitral valve area, from 1·3 cm^2 to 1·5 cm^2, was found to have developed thrombus in the body of the left atrium at follow up, in addition to the persistence of spontaneous echo contrast. A third study six weeks later after the start of warfarin showed complete resolution of thrombus.

CARDIOVERSION

Transthoracic echocardiography was negative in all patients. Four patients were shown to have left atrial spontaneous echo contrast by transoesophageal echocardiography, including both patients with mitral prostheses and one of three patients with mitral stenosis. Only one of nine patients with non-valvar atrial fibrillation had left atrial spontaneous echo contrast. No patient had left atrial thrombus. Cardioversion was performed within 24 hours of echocardiography in all patients and was successful in 11 patients. There were no embolic complications.

ANTICOAGULATION

At the time of initial study 41 of the 100 patients had been treated with anticoagulants for at least one week, including 22 treated for at least one month. Fourteen of these 41 patients (34%) were found to have left atrial or left ventricular thrombus by transoesophageal echocardiography compared with 4/59 (7%) not receiving such treatment. Twenty (45%) of these 41 patients had left atrial or left ventricular spontaneous echo contrast by transoesophageal echocardiography compared with 15/59 (25%) not receiving such treatment.

Discussion

The management of cerebral ischaemic events is hindered by difficulty in clinically distinguishing cardiogenic embolism from other ischaemic events.[18 19] The clinical features of cardiogenic embolism can overlap with local artery-to-artery embolism, and about a third of patients found to have a potential cardiac source of embolism after a cerebral ischaemic event also have cerebrovascular atherosclerosis.[1] Similar diagnosis difficulties arise with peripheral ischaemic events.[3] Further, the detection of potential cardiac sources of embolism, particularly left atrial thrombi, is limited by the low sensitivity of current imaging techniques. Clinical and necropsy studies suggest that embolism from left atrial thrombi accounts for 50–70% of cerebral ischaemic events in patients with non-valvar atrial fibrillation.[20] Non-valvar atrial fibrillation is the most common cardiac condition implicated in presumed embolic stroke, with a fivefold increase in stroke risk compared with sinus rhythm.[20]

Although surgical series show that a large proportion of left atrial thrombi are located in the appendage,[21 22] this structure is difficult to image with transthoracic echocardiography and thrombi in the left atrial appendage are rarely detected by this method.[21 22] In contrast, transoesophageal echocardiography provides high frequency, close range imaging of the left atrium and appendage, which allows visualisation of thrombus, spontaneous contrast, and other abnormalities.[8 10]

Our results confirm the improved yield of potential sources of embolism with transoesophageal echocardiography, particularly for left atrial thrombi ($p < 0·005$) and left atrial spontaneous echo contrast ($p < 0·0001$). Twelve of the 13 left atrial thrombi were found in patients with atrial fibrillation and in the 53 patients in atrial fibrillation transoesophageal echocardiography showed potential embolic sources in 36 but transthoracic echocardiography showed them in only one ($p < 0·0001$).

In our group of 63 patients referred after suspected cardiogenic embolism, we detected a potential embolic source by transoesophageal echocardiography in 27 patients (43%) compared with three (5%) (including one false positive) by transthoracic echocardiography ($p < 0·0001$). In 12 of these patients intracardiac thrombus was detected only by transoesophageal echocardiography, and this resulted in warfarin treatment being started in two patients. The high yield of abnormal findings is related to our patient selection; we included patients with clinically suspected cardiogenic embolism and in whom transthoracic echocardiography alone was considered unlikely to detect potential embolic sources. In comparison, the incidence of thrombi detected by transoesophageal echocardiography in unselected patients with cerebral ischaemic events was 0–4%.[11,23] Selection of patients for transoesophageal echocardiography should take into account both the likelihood of an abnormal finding and the potential impact on patient management.

Left atrial spontaneous echo contrast has recently attracted interest as a marker of thromboembolism.[14] Earlier work suggested that spontaneous echo contrast is caused by aggregates of red cells in low flow states;[24,25] platelets too may also be involved.[26] Most patients with left atrial thrombi also have left atrial spontaneous contrast;[14] this was found in 10 of 13 patients in our series. Thus spontaneous echo contrast may prove to be a useful marker of sluggish blood flow—a condition favouring thrombus formation. In vitro data suggest that spontaneous echo contrast is not prevented by anticoagulant treatment.[24] Indeed we found a higher incidence of both thrombi and spontaneous echo contrast in patients receiving warfarin, reflecting associated conditions such as atrial fibrillation, mitral valve replacement, and recent embolism.

We also studied patients before percutaneous balloon dilatation of the mitral valve and DC cardioversion of atrial fibrillation—both procedures with a risk of cardiogenic embolism. Half of the patients in our series with both atrial fibrillation and mitral stenosis were found to have previously unrecognised thrombi in the left atrial appendage; their discovery led to important changes in management. In addition, balloon dilatation of the mitral valve was performed without embolic complications in all patients without evidence of left atrial thrombus. We now perform transoesophageal echocardiography as a routine procedure before percutaneous balloon dilatation of the mitral valve.

There are no previous reports of the effect of balloon dilatation of the mitral valve on left atrial thrombi or spontaneous echo contrast, although disappearance of spontaneous contrast after mitral valve replacement has been reported.[13] We found that left atrial spontaneous echo contrast disappeared in patients with the largest increase in mitral valve area—that is, a mitral valve area of at least 2 cm^2. This is consistent with the reported association between left atrial spontaneous contrast and low left atrial flow rates.[13]

Successful balloon dilatation of the mitral valve also resulted in resolution of or reduction of left atrial appendage thrombi in three patients. However, one patient with atrial fibrillation and a mitral valve area of 1·5 cm^2 who was not receiving warfarin developed a thrombus in the main left atrial cavity after balloon dilatation of the mitral valve.

Cardioversion of atrial fibrillation also carries a small risk of major systemic embolism, even with prior anticoagulation.[5] A method of detecting left atrial thrombi or perhaps dense spontaneous echo contrast before cardioversion may allow the procedure to be timed more appropriately and the need for anticoagulation to be better assessed. In this series all patients in whom transoesophageal echocardiography did not show left atrial thrombus underwent cardioversion without embolic complications.

Our selection criteria limit extrapolation of our findings to all patients after stroke or transient ischaemic attack. Those who interpreted the transoesophageal echocardiographic results were not formally blinded to the transthoracic results. However, the studies were performed and reported independently and prospectively by separate experienced operators. Single plane transoesophageal echocardiography does not optimally visualise the left ventricular apex, which is in the far field of view, and small apical thrombi may be missed. Finally, there are few data on the correlation of echocardiographic and pathological findings for left atrial thrombi, although a preliminary report showed high sensitivity and specificity compared with surgical findings.[27]

Future indications for transoesophageal echocardiography may include the assessment of left atrial thrombi and spontaneous echo contrast in patients with non-valvar atrial fibrillation without previous embolism, in whom the risk of stroke is fivefold higher than in patients in sinus rhythm.[20] There has been controversy about the role of long term anticoagulant therapy in these patients, though recent evidence suggests that warfarin treatment may be beneficial.[28] Because anticoagulant therapy is associated with considerable morbidity and occasional mortality, it would be useful to be able to select patients at higher risk of thromboembolic complications. Transoesophageal echocardiography may provide a method of identifying these patients.

We conclude that transoesophageal echocardiography is a safe procedure that is more sensitive than transthoracic echocardiography for the detection of potential cardiac sources of embolism, particularly in patients with atrial fibrillation. Transoesophageal echocardiography is also useful in screening selected patients at risk of cardiogenic embolism. Further work is required regarding the prognostic implications of transoesophageal echocardiographic findings, such as spontaneous echo contrast, especially in patients with nonvalvar atrial fibrillation.

1 Cerebral Embolism Task Force Cardiogenic Brain Embolism. *Arch Neurol* 1989,46:727–43
2 Wolf PA, Dawber TR, Thomas HE, Kannel WB Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study *Neurology* 1978,28: 973–7
3 Dregelid EB, Stangeland LB, Eide GE, Trippestad A Characteristics of patients operated on because of suspected arterial embolism: a multivariate analysis. *Surgery* 1988;104:530–6.
4 Nishimura RA, Holmes DR Jr, Reeder GS. Percutaneous balloon valuloplasty. *Mayo Clin Proc* 1990,65:198–220

5 Mancini JGB, Goldberger AL. Cardioversion of atrial fibrillation: consideration of embolization, anticoagulation, prophylactic pacemaker, and long-term success. *Am Heart J* 1982;**104**:617–21.

6 Lovett JL, Sandok BA, Giulani ER, Nasser FN. Two-dimensional echocardiography in patients with focal cerebral ischemia. *Ann Intern Med* 1981;**95**:1–4.

7 Knopman DS, Anderson DC, Asinger RW, Greenland P, Mikell F, Good DC. Indications for echocardiography in patients with ischemic stroke. *Neurology* 1982;**32**: 1005–11.

8 Aschenberg W, Schluter M, Kremer P, Schroder E, Siglow V, Bleifeld W. Transoesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. *J Am Coll Cardiol* 1986;**7**:163–6.

9 Zenker G, Erbel R, Kramer G, *et al*. Transoesophageal two-dimensional echocardiography in young patients with cerebral ischemic events. *Stroke* 1988;**19**:345–8.

10 Daniel WG, Angermann C, Engberding R, *et al*. Transoesophageal echocardiography in patients with cerebral ischemic events and arterial embolism—a European Multicenter Study [abstract]. *Circulation* 1989;**80**(suppl II):II–473.

11 Pop G, Sutherland GR, Koudstaal PJ, Sit TW, de Jong G, Roelandt JRTC. Transoesophageal echocardiography in the detection of intracardiac embolic sources in patients with transient ischemic attacks. *Stroke* 1990;**21**:560–5.

12 Seward JB, Khandheria BK, Oh JK, *et al*. Transoesophageal echocardiography: technique, anatomic correlations, implementation and clinical applications. *Mayo Clin Proc* 1988;**63**:649–80.

13 Beppu S, Nimura Y, Sakakibara H, *et al*. Smoke-like echo in the left atrial cavity in mitral valve disease: Its features and significance. *J Am Coll Cardiol* 1985;**6**:744–9.

14 Daniel WG, Nellessen U, Schroder E, *et al*. Left atrial spontaneous echo contrast in mitral valve disease: an indicator for an increased thromboembolic risk. *J Am Coll Cardiol* 1988;**11**:1204–11.

15 Hatle L, Angelsen B, Tromsdal A. Non-invasive assessment of atrioventricular pressure half-time by Doppler ultrasound. *Circulation* 1979;**60**:1096–104.

16 Lechat P, Mas JL, Lascault G, *et al*. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988; **318**:1148–52.

17 Nobuyoshi M, Hamasaki N, Kimura T, *et al*. Indications, complications, and short-term clinical outcome of percutaneous transvenous mitral commissurotomy. *Circulation* 1989;**80**:782–92.

18 Humphrey PRD, Harrison MJG. How often can an embolic stroke be diagnosed clinically? A clinicopathological correlation. *Postgrad Med J* 1985;**61**:1039–42.

19 Ramirez-Lassepas M, Cipolle RJ, Bjork RJ, *et al*. Can embolic stroke be diagnosed in the basis of neurologic clinical criteria? *Arch Neurol* 1987;**44**:87–9.

20 Sherman DG, Dyken ML, Fisher M, Harrison MJG, Hart RG. Cerebral embolism. *Chest* 1986;**89**(suppl 2): 82S–98S.

21 Shrestha NK, Moreno FL, Narciso FV, Torres L, Calleja HB. Two-dimensional echocardiographic diagnosis of left atrial thrombus in rheumatic heart disease. A clinicopathologic study. *Circulation* 1983;**67**:341–7.

22 Bansal RC, Heywood JT, Applegate PM, Jutzy KR. Detection of left atrial thrombi by two-dimensional echocardiography and surgical correlation in 148 patients with mitral valve disease. *Am J Cardiol* 1989;**64**:243–6.

23 Jacobs NH, Whyte S, Kelleher AD, Juarez CC, Garrick R, Feneley MP. Limited role of transesophageal echocardiography in unselected patients with cerebral ischaemic events [abstract]. *Circulation* 1990;**82**(suppl III):III–110.

24 Sigel B, Coelho JCU, Spigos DG, *et al*. Ultrasonography of blood during stasis and coagulation. *Invest Radiol* 1981; **16**:71–6.

25 Mikell FL, Asinger RW, Elsperger KJ, Anderson WR, Hodges M. Regional stasis of blood in the dysfunctional left ventricle: echocardiographic detection and differentiation from early thrombosis. *Circulation* 1982;**66**:755–63.

26 Mahoney C, Sublett KL, Harrison MR. Resolution of spontaneous contrast with platelet disaggregatory therapy (trifluoperazine). *Am J Cardiol* 1989;**63**:1009–10.

27 Matsumura M, Shah P, Kyo S, Omoto R. Advantages of transesophageal echo for correct diagnosis on small left atrial thrombi in mitral stenosis [abstract]. *Circulation* 1989;**80**(suppl II):II–678.

28 Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: The Copenhagen AFASAK study. *Lancet* 1989;**i**:175–9.

Obituary

EIRIAN WILLIAMS

Bill Williams, MD, FRCP, died on 31 March, aged 65, after a long struggle against an aggressive prostatic carcinoma. He spent 30 years as physician in general medicine and cardiology at Withybush Hospital, Haverfordwest, Pembrokeshire. He was a member of the Association of Physicians of Great Britain and Ireland and of the British Cardiac Society.

He was an international authority on brucellosis and published several papers on this topic in the *Lancet* in the 1970s. It was appropriate that he was asked to give the Donald Hunter Memorial Lecture to the Royal College of Physicians on this topic since Hunter was one of his mentors at the London Hospital and a lifelong friend.

Apart from being a dedicated and gifted clinician his main achievement was the creation of Withybush General Hospital in Haverfordwest, Pembrokeshire, which resulted out of his single-minded efforts. His contributions to postgraduate medicine in the area were recognised when the library in the postgraduate centre was named after him.

He will be remembered with affection by his many friends as an accomplished gardener, no mean wet fly fisher, and as a man who never gave up a cause—be it the developmment of his hospital or of academic cardiology in Cardiff. He is survived by his wife, three children, and seven grandchildren.

REG HALL

Br Heart J 1991;66:308–12

DiGeorge syndrome with isolated aortic coarctation and isolated ventricular septal defect in three sibs with a 22q11 deletion of maternal origin

D I Wilson, I E Cross, J A Goodship, S Coulthard, A H Carey, P J Scambler, H H Bain, A S Hunter, P E Carter, J Burn

Department of Human Genetics, University of Newcastle upon Tyne
D I Wilson
I E Cross
J A Goodship
S Coulthard
J Burn

Department of Biochemistry and Molecular Genetics, St Mary's Hospital Medical School, London
A H Carey
P J Scambler

Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne
H H Bain
A S Hunter

Department of Paediatrics, West Cumberland Hospital, Cumbria
P E Carter

Correspondence to
Dr D I Wilson, Department of Human Genetics,
19 Claremont Place,
Newcastle upon Tyne
NE2 4AA

Accepted for publication
4 July 1991

Abstract

DiGeorge syndrome was diagnosed in an infant who had an interrupted aortic arch, hypoparathyroidism, and low T lymphocyte numbers. Two siblings had heart defects that are not commonly described in DiGeorge syndrome (a membranous ventricular septal defect and coarctation of the aorta respectively). These siblings did not have evidence of thymic dysfunction or hypoparathyroidism. Chromosome analysis showed that the mother, whose cardiovascular examination was normal, and her three offspring with heart defects had a 22q11 interstitial deletion, which was confirmed by molecular analysis.

This family suggests that 22q11 deletions can cause apparently isolated heart defects and that the range of these defects may be wider than previously recognised. Once the genes that are deleted in this family are characterised they will be useful candidate genes in the investigation of isolated cardiac malformations.

Though genetic defects are known to be a major cause of heart malformation the precise relation is poorly understood. One approach to the search for the genetic basis of heart defects is via syndromes with known chromosomal localisations.

In 1965 DiGeorge described congenital absence of the thymus and parathyroid glands found at necropsy in three children, and in a fourth child with congenital hypoparathyroidism and defective cellular immunity.[1] In subsequent years it was recognised that congenital heart defects and a characteristic facial appearance were often associated with these findings.[2 3] The combination of aplasia, or hypoplasia, of the thymus and parathyroid glands together with cardiac defects and dysmorphic facial features became known as DiGeorge syndrome.

The cardiac defects most commonly found in DiGeorge syndrome are interrupted aortic arch type B and truncus arteriosus.[4–6] Type B interrupted aortic arch occurs in over 30% of cases of DiGeorge syndrome, truncus arteriosus in 25% of cases, and tetralogy of Fallot in 20%.[7] An aberrant right subclavian artery arising from the descending aorta, a right sided aortic arch, and transposition of the great arteries are also well recognised cardiac abnormalities in DiGeorge syndrome.

The dysmorphic features seen in the syndrome are hypertelorism with short palpebral fissures, a small mouth and short philtrum, retrognathia, and low set, posteriorly rotated ears.[2]

In 1981 de la Chapelle described a family with members carrying a balanced chromosome rearrangement, t(20;22)(q11;q11). Four children in this pedigree had DiGeorge syndrome; all had the same unbalanced translocation products resulting in monosomy for 22pter-22q11 and trisomy for 20pter-20q11.[8] The following year a further three unrelated patients with DiGeorge syndrome were reported who were monosomic for 22pter-22q11.[9] Two of these children had inherited unbalanced forms of familial translocations and the third child had a de novo unbalanced translocation. There have been additional reports of affected children with unbalanced translocations with chromosome 22 involvement.[10–13] The minimal region of deletion common to all these cases is 22q11. More recently a child with DiGeorge syndrome and an interstitial deletion of 22q11 has been described.[14]

We report a family in which an interstitial deletion of 22q11 was transmitted from a mother to three offspring. One child has the complete DiGeorge syndrome phenotype. The remaining three individuals with the cytogenetic deletion have a range of clinical features but none fulfils the diagnostic criteria of DiGeorge syndrome.

Patients and methods

CASE 1

The proposita, the youngest member of the sibship, was born at 40 weeks' gestation and weighed 2·46 kg. She had bilateral talipes equinovarus and a dysmorphic appearance with small mouth, short philtrum, and low set posteriorly rotated ears (fig 1). She became unwell at three days of age with poor peripheral perfusion and cardiac failure. Echocardiography showed an interrupted aortic arch type B and a perimembranous ventricular septal defect. The total blood T lymphocyte count was low (580 × 10^6/l, reference values > 1500 × 10^6/l). Surgical repair and patch closure of the ventricular septal defect were performed. The postoperative period was complicated by necrotising enterocolitis and

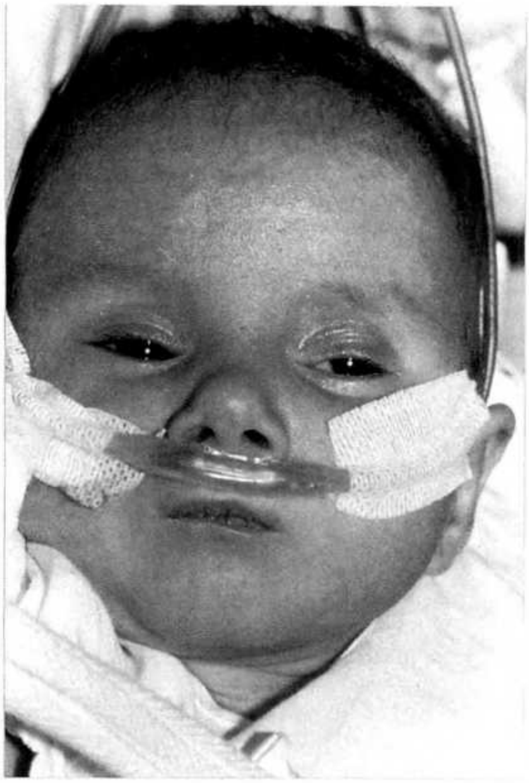


Figure 1 Small mouth and short philtrum in case 1.

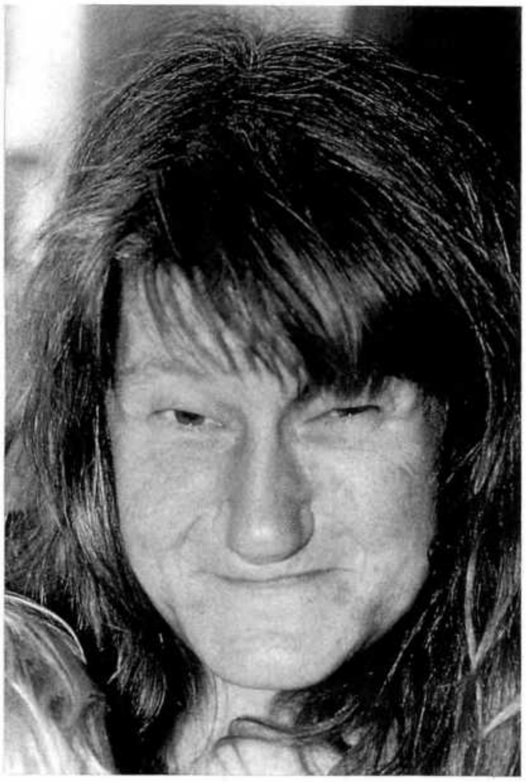


Figure 2 Short philtrum and narrow upslanting palpebral fissures in the mother.

hypocalcaemic seizures (total serum calcium 1·15 mmol/l, normal range 2·28–2·65 mmol/l). She was given calcium supplementation until she was six weeks old. Renal ultrasound showed that she had no left kidney.

The parents were unrelated white Europeans. Neither had a history of frequent infections, seizures, or heart disease in childhood. Clinical examination of the cardiovascular system in both parents was normal; they declined further cardiological investigation. The mother was mildly dysmorphic having a short philtrum and narrow upslanting palpebral fissures (fig 2). Her four pregnancies were uncomplicated. Alcohol and drug ingestion during these pregnancies was denied and there was no history of pregnancy loss. The first child, born at 40 weeks' gestation weighing 3·5 kg, was well and not dysmorphic. Their other two children had undergone surgical correction of heart malformations.

CASE 2

The second child was born at 41 weeks' gestation and weighed 2·53 kg. He was dysmorphic, with narrow palpebral fissures and a high arched palate (fig 3), and had a right inguinal hernia. He presented with failure to thrive at two months of age and was found to have a membranous ventricular septal defect. This was confirmed by echocardiography and cardiac catheterisation. The ventricular septal defect required surgical repair when he was 4 years old. At 11 years of age he had had no symptoms of immunodeficiency or hypocalcaemia and his serum calcium concentration and total blood T lymphocyte count were within normal limits.

CASE 3

The third child was born at 39 weeks' gestation and weighed 2·9 kg (fig 4). He had a small mouth, poorly modelled philtrum, overfolded pinnae, and bilateral talipes equinovarus. Bilateral inguinal hernias were repaired at 7 days of age. He did not thrive postoperatively and coarctation of the aorta and a persistent ductus arteriosus were diagnosed when he was 4 weeks old. At operation a hypoplastic isthmus was identified between the left carotid

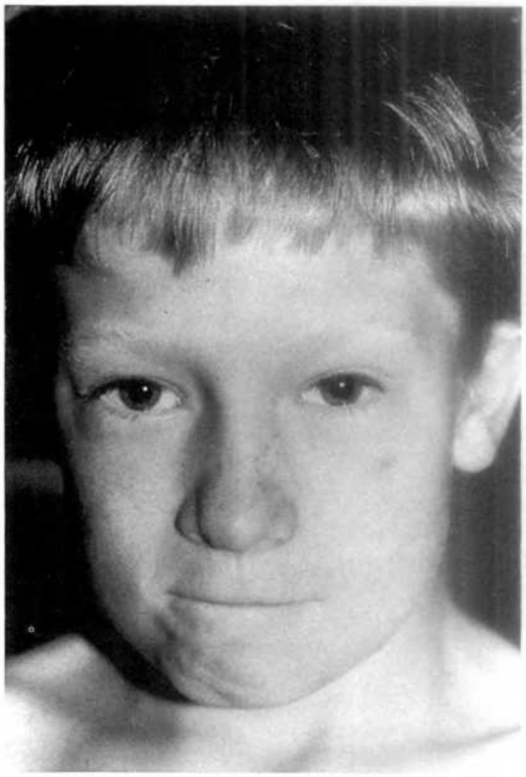


Figure 3 Narrow palpebral fissures in case 2.

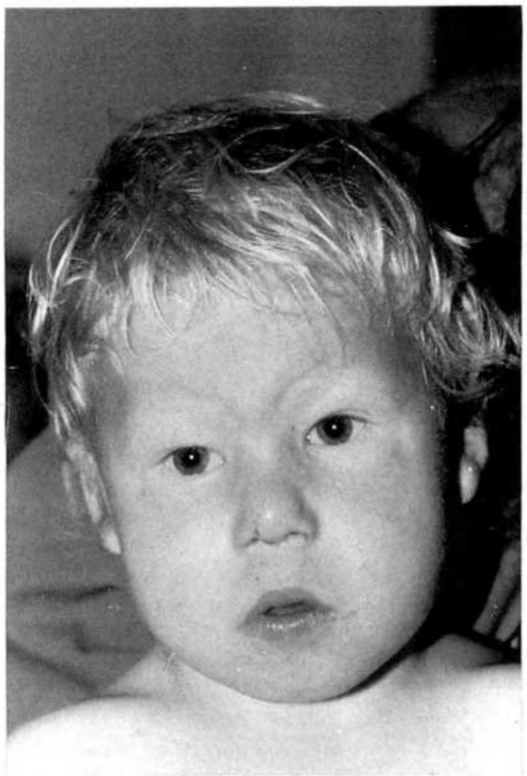


Figure 4 Small mouth and poorly modelled philtrum in case 3.

artery and the left subclavian artery. This was repaired and the ductus arteriosus was ligated. Twenty four hours after the operation routine biochemical investigations showed that his serum calcium was 2·06 mmol/l (reference range 2·28–2·65 mmol/l). He was symptom free and the serum calcium returned to the normal range within 48 hours without specific treatment. He had two seizures two weeks after the thoracotomy. Blood glucose, calcium, and magnesium were normal at the time of these seizures and no cause was identified. At the age of 4 he was well and his T lymphocyte and calcium values were within normal limits.

CYTOGENETIC STUDIES

Chromosome preparations were made from 72 hour phytohaemagglutinin stimulated cell cultures from peripheral blood from members of the family. Cultures were synchronised by a pulse of thymidine administered 21 hours before harvesting. Colcemid was added for only 8–15 minutes before harvesting to obtain chromosomes of sufficiently high resolution to visualise band 22q11.22—that is at least 850 bands per haploid set.[15] Preparations were G banded with trypsin and Leishman stain.

Chromosome analysis showed apparently normal karyotypes in the father and eldest daughter of the family. The mother and the remaining three children (cases 1, 2, and 3) had a small interstitial deletion of the proximal long arm of chromosome 22, del(22)(q11.21q11.23) (fig 5).

MOLECULAR STUDIES

Quantitative Southern blot analysis was carried out with the probe KI-182·3 (D22S134) which was generated from the flow-sort-enriched chromosome 22 library LL22NSO1 and localised to the region deleted in DiGeorge syndrome patients.[16]

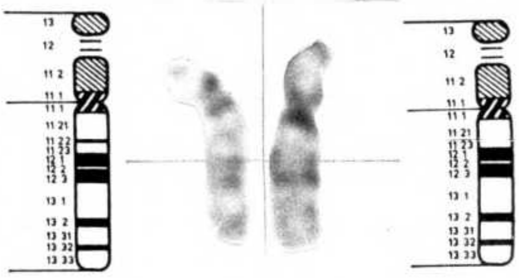


Figure 5 Chromosome 22 photomicrographs from case 2 with adjacent ideograms. The normal chromosome is on the left and the deleted chromosome on the right. Band q11.22 is absent from the chromosome on the right.

DNA was extracted from venous blood by salting out[17] and digested with *Pvu*II. Electrophoresis was carried out through a 0·8% agarose gel at 2 volts/cm for 18 hours. The DNA was transferred to Hybond N+ membrane (Amersham International) by alkali blotting following the manufacturer's protocol. Probes were labelled by random priming.[18] The filter was hybridised with KI-182·3 and a rhodopsin control probe. Hybridisation and washing conditions were as described previously.[16]

The signal intensity with KI-182·3 in the father and eldest child in the sibship was comparable to that in equally loaded control lanes. The KI-182·3 signal intensity in the mother and in cases 1, 2, and 3 was half the intensity in normal control tracks with equal DNA loading (fig 6). This was confirmed by laser densitometry.

Discussion

Four members of this family have an interstitial deletion at chromosome 22q11. The youngest child fulfills the clinical criteria for the diagnosis of DiGeorge syndrome. She had a typical heart defect, hypocalcaemia, low T lymphocyte numbers, and the dysmorphic features associated with the condition. Her mother and two of her siblings have the same cytogenetic deletion but do not have DiGeorge syndrome.

The molecular analysis of DNA from this family confirms the cytogenetic findings. The KI-182·3 signal intensity in the father and normal sister were equivalent to the normal control sample showing the presence of two copies of the DNA sequence. The signal intensity in the mother, proposita, and her siblings with congenital heart disease was half that in the equivalent normal control track showing that they have only one copy of KI-182·3 (D22S134). Thus a deletion of chromosome 22q11 was demonstrated by two independent methods in the proposita, her mother, and the two siblings with congenital heart disease.

A common feature in the range of cardiovascular malformations in DiGeorge syndrome is a disturbance of the outflow tract of the embryonic heart or impaired development of

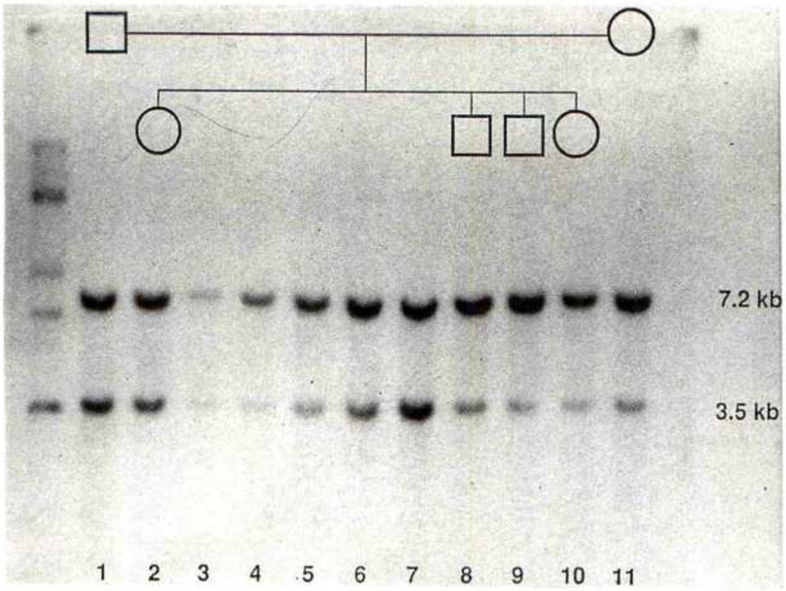


Figure 6 Autoradiograph showing the quantitative Southern blot analysis. The KI-182·3 band is at 3·5 kb and the control band at 7·2 kb. Tracks 3 to 7 contain 3 μg, 5 μg, 7 μg, 9 μg, and 11 μg of DNA from a normal control. Track 1 is DNA from the father, track 2 from the oldest (normal) child in the sibship, track 8 from case 2, track 9 from case 3, track 10 from case 1 and track 11 from the mother. The intensity of the KI-182·3 band in the father and eldest child is comparable with that in the normal control. The intensity of the KI-182·3 band is clearly reduced in the mother, case 1, case 2, and case 3.

the branchial arch arteries or both. Clinical examination of the cardiovascular system in the mother was normal, though this does not exclude congenital heart defects. The heart defects in the brothers were an isolated membranous ventricular septal defect and a coarctation of the aorta. While ventricular septal defects are commonly found in DiGeorge syndrome in association with other cardiac abnormalities they are unusual as an isolated finding.[4,7] We found only one previous report of coarctation of the aorta in DiGeorge syndrome.[19]

The older boy (case 2) did not have any signs of hypocalcaemia at any stage. His serum calcium was not measured in the neonatal period, but after surgical repair of his ventricular septal defect his serum calcium remained within the normal range. In case 3 serum calcium was found to be slightly low after cardiac surgery but returned to normal quickly without specific treatment. Transient hypocalcaemia is often seen after cardiac surgery in children and can be non-specific. There was no history of symptoms of hypocalcaemia in the mother.

The index case had the characteristic dysmorphic appearance seen in DiGeorge syndrome. However, the facial features in patients with DiGeorge syndrome are subtle and variable. The mildly dysmorphic appearance of the mother and other affected siblings was compatible with DiGeorge syndrome.

DiGeorge originally described children with an immunodeficiency and the index case had a low T lymphocyte count. T lymphocyte numbers were not measured at the time of presentation in her siblings but were within normal limits later in childhood and they had not had recurrent infections. This suggests that they did not have important thymic involvement.

De la Chapelle described four affected individuals in one family in which a 20;22 translocation was segregating.[8] Greenberg *et al* reported a case of DiGeorge syndrome associated with partial monosomy of 22q resulting from an unbalanced translocation, der(22),t(4;22)(q35.2;q11.2).[20] The first child in the sibship described by Greenberg had died at two months and was thought to have had a congenital heart defect; the second child was found at necropsy to have truncus arteriosus, thymic aplasia and parathyroid hypoplasia; and the third child was the proband. The mother was found to carry the same unbalanced chromosome rearrangement. Cardiovascular examination was normal but she was noted to have hypertelorism and on investigation she had low T lymphocyte numbers and a reduced response to T cell mitogens compared with a normal control. Augusseau *et al* reported a family in which a phenotypically normal female with a balanced translocation (46,XX,t(2;22)(q14;q11)) had a child with the same karyotype with hypertelorism, micrognathia, severe coarctation of the aorta, and hypocalcaemia.[19] The woman's sister carried the same translocation and had one pregnancy terminated because of a fetal cardiac malformation. It is possible that a further chromosome rearrangement may have occurred and led to the different phenotype in the children reported by Augusseau and Greenberg. However, it is more likely that the same cytogenetic abnormality resulted in differing phenotypes within families—both in these families and in the family we have presented here.

There have been previous reports of DiGeorge syndrome occurring in more than one individual in families with no detectable cytogenetic abnormality. Rohn *et al* described a family in which a father and two male offspring had features of DiGeorge syndrome.[21] Both infants had truncus arteriosus, hypocalcaemia, T lymphocyte dysfunction, and facial features typical of DiGeorge syndrome. Their father was mildly dysmorphic and had an abnormal parathyroid response to a phosphate loading test but a normal cardiovascular system. Chromosome analysis in the father and his sons was normal but a molecular deletion of 22q11 has recently been detected in the second child in this sibship.[22] Keppen *et al* have described another family with dominant transmission where cytogenetic analysis did not show any abnormality.[23] The infant in this family had an interrupted aortic arch type B and hypocalcaemia. His father had a history of neonatal seizures secondary to hypocalcaemia, recurrent infections throughout his life, and cardiac catheterisation at the age of 14 had shown a right sided aortic arch. There is now evidence of a molecular deletion of 22q11 in this man.[22] A family of three children with truncus arteriosus, hypocalcaemia, and hypoplasia of the thymus and clinically normal parents has been reported.[24] The authors suggested autosomal recessive inheritance in this family but an alternative explanation would be non-penetrance, as occurred in the present report, or a group of cells with a new dominant mutation in the gonads of one of the parents—that is, germline mosaicism.

DiGeorge syndrome is a clinical diagnosis based on finding evidence of thymic and parathyroid hypoplasia, outflow tract defects of the heart, and a dysmorphic appearance. In the family we present, the cytogenetic deletion associated with DiGeorge syndrome caused a wide variation in phenotype. The youngest girl has all four features of DiGeorge syndrome. The two boys have heart defects which are not often found in DiGeorge syndrome and the mother has no apparent cardiac abnormality. The phenotypic variation in this family and the families discussed above is evidence against DiGeorge syndrome being a contiguous gene defect. Both in the familial cases in which no cytogenetic abnormality was identified and in the families reported by Greenberg, Augusseau, and ourselves where individuals with the same apparent cytogenetic abnormality have different phenotypes the parent has the mildest phenotype and does not fulfil the diagnostic criteria of DiGeorge syndrome. It is clearly important to exclude clinical and cytogenetic abnormalities in parents of children with complete DiGeorge syndrome. In the past individuals with the milder end of the clinical spectrum were more likely to have reproduced than those with complete DiGeorge syndrome. The incidence of DiGeorge syndrome in offspring of affected individuals may, in part, be answered by the British Heart Foundation study of offspring.[25]

The findings in this family suggest that in some individuals with isolated heart defects, including ventricular septal defects or coarctations, the cause of the heart defect is a deletion of chromosome 22q11. This has obvious implications for the risk of recurrence in their offspring.

This work was supported by grants from the British Heart Foundation and the Borwick Trust We also thank Mrs J Brown who carried out chromosome analysis in two of the family members Dr J Nathans kindly provided the rhodopsin probe used as the control probe in the dosage experiments. We obtained written permission from the family for publication of the photographs.

1 Cooper MD, Peterson RDA, Good RA A new concept of the cellular basis of immunity *J Pediatr* 1965,67:907–8
2 Freedom RM, Rosen FS, Nadas AS Congenital cardiovascular disease and anomalies of the third and fourth pharyngeal pouch. *Circulation* 1972,46 165–72.
3 Finley JP, Collins GF, De Chadarevian JP, Williams RL. DiGeorge syndrome presenting as severe congenital heart disease in the newborn. *Can Med Assoc J* 1977,116: 635–40
4 Conley ME, Beckwith JB, Mancer JFK, Tenckhoff L. The spectrum of the DiGeorge syndrome. *J Pediatr* 1979,94· 883–90
5 Moerman P, Goddeeris P, Lauwerijns J, Van Der Hauwaert LG Cardiovascular malformations in DiGeorge syndrome (congenital absence or hypoplasia of the thymus). *Br Heart J* 1980,44:452–9
6 Moerman P, Dumoulin M, Lauweryns J, Van Der Hauwaert LG. Interrupted right aortic arch in DiGeorge syndrome *Br Heart J* 1987,58·274–8.
7 Van Mierop LHS, Kutsche LM Cardiovascular anomalies in DiGeorge syndrome and importance of neural crest as a possible pathogenetic factor. *Am J Cardiol* 1986,58:133–7
8 De la Chapelle A, Herva R, Koivisto M, Aula P. A deletion in chromosome 22 can cause DiGeorge syndrome *Hum Genet* 1981,57 253–6
9 Kelley RI, Zackai EH, Emanuel BS, Kistenmacher M, Greenberg F, Punnett HH The association of the DiGeorge anomalad with partial monosomy of chromosome 22 *J Pediatr* 1982,101·197–200
10 Schwanitz G, Zerres K. Partial monosomy 22 as result of an X/22 translocation in a newborn with DiGeorge syndrome. *Ann Genet* 1987,30:80–4.
11 Faed MJW, Robertson J, Swanson Beck J, Cater JI, Bose B, Madlom MM. Features of diGeorge syndrome in a child with 45,XX,-3,-22,+der(3),t(3,22)(p25;q11). *J Med Genet* 1987,24 225–34
12 Dallapiccola B, Marino B, Giannotti A, Valorani G DiGeorge anomaly associated with partial deletion of chromosome 22: report of a case with X/22 translocation and review of the literature. *Ann Genet* 1989,32.92–6.
13 Anneren G, Gustafsson J, Sunnegardh J DiGeorge syndrome in a child with partial monosomy of chromosome 22 *Ups J Med Sci* 1989;94·47–53.
14 Mascarello JT, Bastian JF, Jones MC. Interstitial deletion of chromosome 22 in a patient with the diGeorge malformation sequence *Am J Med Genet* 1989;32·112–4.
15 Standing Committee on Human Cytogenetic Nomenclature. *An international system for human cytogenetic nomenclature (1985)* Basle S Karger, 1985
16 Carey AH, Roach S, Williamson R, *et al* Localization of 27 DNA markers to the region of human chromosome 22q11-pter deleted in patients with the DiGeorge syndrome and duplicated in the der22 syndrome. *Genomics* 1990;7. 299–306.
17 Miller SA, Dykes DD, Polesky HF A simple salting out procedure for extracting DNA from human nucleated cells *Nucleic Acids Res* 1988;16.1215.
18 Feinberg AP, Vogelstein B. A technique for radiolabelling DNA restriction endonuclease fragments to high specific activity *Anal Biochem* 1984,137 266–7
19 Augusseau S, Jouk S, Jalbert P, Prieur M. DiGeorge syndrome and 22q11 rearrangements *Hum Genet* 1986; 74 206
20 Greenberg F, Crowder WE, Paschall V, Colon-Linares J, Lubianski B, Ledbetter DH Familial DiGeorge syndrome and associated partial monosomy of chromosome 22 *Hum Genet* 1984,65:317–9
21 Rohn RD, Leffell MS, Leadem P, Johnson D, Rubio T, Emanuel BS. Familial third-fourth pharyngeal pouch syndrome with apparent autosomal dominant transmission *J Pediatr* 1984,105 47–51
22 Scambler PJ, Carey AH, Wyse RKH, *et al.* Microdeletions within 22q11· associated with sporadic and familial DiGeorge syndrome. *Genomics* 1991;10.201–6.
23 Keppen LD, Fasules JW, Burks AW, Gollin SM, Sawyer JR, Miller CH Confirmation of autosomal dominant transmission of the DiGeorge malformation complex. *J Pediatr* 1988,113·506–8
24 Raatikka M, Rapola J, Tuuteri L, Louhimo I, Savilahti E. Familial third and fourth pharyngeal pouch syndrome with truncus arteriosus·DiGeorge syndrome *Pediatrics* 1981,67.173–5
25 Burn J, Coffey R, Little J, *et al* Recurrence risks in the offspring of adults born with major heart defects; first results of a British collaborative study [abstract] *Am J Hum Genet* 1990;47 121

Br Heart J 1991,66:313–5

Silent ischaemia in diabetic men with autonomic neuropathy

J J O'Sullivan, R M Conroy, K MacDonald, T J McKenna, B J Maurer

Abstract

Autonomic neuropathy is associated with an increased incidence of silent myocardial infarction and sudden death. The purpose of this study was to investigate the prevalence of silent myocardial ischaemia in diabetic patients with autonomic neuropathy and without. Five standard autonomic function tests were performed on 41 men with diabetes: postural change in blood pressure, postural change in heart rate, heart rate response to deep breathing, heart rate response to Valsalva's manoeuvre, and blood pressure response to sustained handgrip. There were 17 patients with autonomic neuropathy (group A) and 24 with normal autonomic function (group B). All patients underwent 24 hour ambulatory electrocardiographic monitoring to detect silent ischaemia. There was no significant difference in risk factors for coronary artery disease or history of angina pectoris between these groups. The prevalence of silent ischaemia was 64·7% in group A (95% confidence interval (95% CI) 38·33 to 85·79%) and 4·1% in group B (95% CI 0·11 to 21·12%). This represents a relative risk of 42·2 (95% CI 4·5 to 39·4, $p < 0·001$). These results are consistent with the concept that autonomic neuropathy may prevent the development of anginal pain and thus obscure the presence of ischaemic heart disease.

Twenty four hour ambulatory electrocardiographic monitoring may identify a subgroup of diabetic patients with autonomic neuropathy who have myocardial ischaemia and to whom treatment may be offered.

Clinical evidence of autonomic neuropathy in patients with diabetes mellitus is associated with increased mortality.[1] Many of these deaths are sudden and may be due to myocardial ischaemia.[2,3] Asymptomatic (silent) myocardial infarction is more common in diabetic patients with autonomic neuropathy than in those without neuropathy[4] but the prevalence of silent myocardial ischaemia is unknown. The purpose of this study was to investigate the prevalence of silent ischaemia, as detected by ambulatory electrocardiographic monitoring, in diabetic men with and without autonomic neuropathy.

Patients and methods

Forty four diabetic men who were recruited from the diabetic clinic, ophthalmology unit, and general medical wards of St Vincent's Hospital participated in the study. We excluded women; men younger than 40 years; patients with an abnormal resting electrocardiogram (bundle branch block, atrial fibrillation, or ST segment abnormalities); patients taking digitalis, β blockers, or antidepressant medication; patients confined to bed; patients unable to give informed consent; patients with myocardial infarction or unstable angina within the past three months; and patients unable adequately to perform the autonomic function tests. We questioned the patients about symptoms of impotence, diarrhoea, disordered sweating, and postural dizziness. Physical examination and urinalysis were performed to identify complications of diabetes. The following five tests of autonomic function were performed and the responses graded as normal, borderline, or abnormal (table 1).

(*a*) *Systolic blood pressure response to standing.*

(*b*) *Heart rate response to standing*—The electrocardiogram was continually recorded as the patient went from lying to standing. After standing, the ratio of the longest RR interval at around the 30th beat to the shortest RR interval around the 15th beat was calculated.

(*c*) *Heart rate variation during deep breathing*—The heart rate was continually recorded while the patient took six deep breaths over a period of one minute. The mean of the difference between the maximum and minimum heart rates was calculated.

(*d*) *Heart rate response to Valsalva's manoeuvre*—The patient blew into a mouthpiece connected to a sphygmomanometer and held

Table 1 Grading of autonomic function tests

	Valsalva's ratio	*Heart beat variation during deep breathing (beats/min)*	*Immediate heart rate lying to standing (30·15)*	*Increase in diastolic blood pressures during sustained handgrip (mm Hg)*	*Postural hypotension (mm Hg)*
Normal	>1·20	>15	>1·03	>15	⩽20
Borderline	1·11-1·20	11-15	1·10-1·03	11-15	21-30
Abnormal	⩽1·10	⩽10	⩽1·01	⩽10	>30

Departments of Cardiology and Endocrinology, St Vincent's Hospital, Dublin, Ireland
J J O'Sullivan
R M Conroy
K MacDonald
T J McKenna
B J Maurer

Correspondence to
Dr J J O'Sullivan,
Department of Paediatric Cardiology, Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN.

Accepted for publication 29 April 1991

it at a pressure of 40 mm Hg for 15 seconds while the heart rate was continually recorded by electrocardiography. We calculated the ratio between the longest RR interval after the manoeuvre to the shortest RR interval during the manoeuvre.

(*e*) *Blood pressure response to sustained handgrip*—Diastolic blood pressure was measured during sustained handgrip every minute over a five minute period.

All patients had 24 hour ambulatory electrocardiographic monitoring. The ambulatory monitor used (Q Med Monitor One) contains a microprocessor that is connected through a single connector to one bipolar lead and a grounding electrode. Significant events were stored in a memory protected by a lithium battery. This system has been validated previously.[5 6] After the electrodes were applied to the precordium a control strip was run for one minute to ensure that signals were satisfactory. The microprocessor was programmed to detect a horizontal or downsloping ST segment of 1 mm or more occurring 60 ms after the J point and persisting for at least 40 s. When the monitoring period was complete we obtained a sample of each ischaemic event and confirmed the presence of ST segment depression. We measured the number of ischaemic episodes and the total duration of ischaemia, if present, in each patient.

Statistical analysis was performed using the IBM SAS system. Differences between means were assessed for significance by the *t* test, and those between proportions by the χ^2 or, in the case of low observed frequencies, Fisher's exact test. Relative risks and their 95% CIs were calculated by the Mantel-Haenszel method as implemented in SAS version 5.[7]

Results

ASSESSMENT OF AUTONOMIC FUNCTION IN DIABETIC MEN

Seventeen patients had at least two abnormal tests and these were designated as having definite autonomic neuropathy (group A). All tests were normal in 24 patients (group B). Three patients with a borderline abnormality in only one test were excluded from further study because they could not be classified as definitely normal or abnormal. The 17 patients with definite autonomic neuropathy had at least two abnormal parasympathetic function tests. All 17 patients had an abnormal heart rate response to standing and deep breathing. Seven subjects had an abnormal response to Valsalva's manoeuvre and five had a borderline result. Only three patients had abnormal sympathetic function (blood pressure response to standing and sustained handgrip), confirming the findings of others[8 9] that sympathetic dysfunction occurs late and virtually always in the presence of abnormal parasympathetic function tests.

CLINICAL CHARACTERISTICS OF PATIENTS WITH AND WITHOUT AUTONOMIC NEUROPATHY

We found no significant differences in age, smoking history, history of hypertension, family history of coronary artery disease, or mean cholesterol concentration between diabetic patients with autonomic neuropathy and without (table 2). Forty one per cent of both groups had a history of angina pectoris. Angina was mild in all patients (grades I or II) except for one patient in group A with grade III symptoms (New York Heart Association). There was no significant difference in antianginal treatment between the groups, with 40% of the neuropathic group and 33% of the non-neuropathic group on either long acting nitrates or calcium channel blockers.

Patients with autonomic neuropathy tended to have had diabetes longer and had more complications than patients without autonomic neuropathy but these differences were not statistically significant. Five patients with autonomic neuropathy had no clinical evidence of peripheral neuropathy, retinopathy, or nephropathy. Fifty eight per cent of the neuropathic group had symptoms that could be attributed to autonomic dysfunction.

SILENT MYOCARDIAL ISCHAEMIA IN DIABETIC PATIENTS WITH AND WITHOUT AUTONOMIC NEUROPATHY

Patients with autonomic neuropathy had a significantly higher incidence of silent ischaemia than patients without. Eleven patients with autonomic neuropathy showed episodes of silent ischaemia, whereas only one patient without neuropathy did so, representing a relative risk of 42·2 (95% CI 4·5 to 39·4,

Table 2 Clinical characteristics of patients with (group A) and without (group B) autonomic neuropathy

Characteristics	*Group A* (*n* = 17)	*Group B* (*n* = 24)	*p Value*
Age (yr, mean)	61	61·3	0·8359
Cigarette smokers (%)	9 (53)	11 (45·8)	0·654
Mean cholesterol (mm/l)	5·6	5·2	0·3086
Family history of coronary disease (%)	4 (23·5)	4 (16·6)	0·587
Hypertension (%)	8 (47)	9 (37·5)	0·541
Previous myocardial infarction (%)	7 (41)	9 (37·5)	0·812
History of angina pectoris (%)	7 (41)	10 (41·6)	0·975
No history of coronary artery disease (%)	8 (47)	12 (50)	0·853
On insulin therapy (%)	6 (35·3)	12 (50)	0·350
On oral hypogycaemic agents (%)	7 (41)	10 (41·6)	0·975
Controlled on diet only (%)	4 (23·5)	2 (8·3)	0·212
Mean duration of diabetes (yr)	8·9	6·2	0·295
Total No of patients with diabetic complications (%)	12 (70·5)	12 (50)	0·187
Peripheral neuropathy (%)	11 (64·7)	9 (37·5)	0·086
Nephropathy (%)	3 (17·6)	2 (18·3)	0·633
Retinopathy (%)	7 (41)	8 (33·3)	0·607

$p < 0\cdot001$). A total of 89 ischaemic episodes occurred, with an average duration of 4·8 minutes in 11 patients with autonomic neuropathy. During the monitoring period there were three episodes of angina in these patients with autonomic neuropathy. One patient with normal autonomic function showed silent ischaemia and had a further episode of angina over the period of monitoring. He had two symptomless episodes of ST segment depression, total duration two minutes. Six of the patients with silent ischaemia in group A had no history of angina pectoris but two had evidence of old infarction on the electrocardiogram. Therefore, four patients with autonomic neuropathy had unsuspected ischaemia.

Discussion

The autonomic nervous system controls the activity of the heart, blood vessels, and smooth muscle throughout the body. Relatively simple and reproducible bedside tests can assess the functional integrity of the sympathetic and parasympathetic divisions.[10 11] In diabetes mellitus damage to the parasympathetic system tends to occur early whereas clinical evidence of dysfunction of the sympathetic system is found later and is often associated with symptoms. Diabetic patients with symptoms and clinical evidence of autonomic neuropathy have a grave prognosis.[1] In one prospective study of 73 patients with abnormal autonomic function tests a 56% mortality at five years was reported.[1] Twenty eight per cent of the deaths were sudden and the exact mechanism of death was not clear. The importance of coronary artery disease in the diabetic population is well recognised and an increased incidence of silent myocardial infarction has been reported.[4] Abnormalities in the autonomic fibres to the heart were found at necropsy in patients dying of painless myocardial infarction.[12] Evidence of myocardial infarction has not been found at necropsy in many of the sudden deaths in patients with autonomic neuropathy[1 2] but this may not be surprising as evidence of fresh infarction is rare in patients with coronary heart disease dying suddenly.

It is well known that episodes of myocardial ischaemia may occur without clinical symptoms. Erikssen drew attention to the prognostic significance of asymptomatic ischaemic changes detected by exercise testing. In a screening study 50 non-diabetic men with silent ischaemia were identified and nine of these died over a follow up of 13·5 years, all but one of them developing angina before death.[13 14] Ambulatory electrocardiographic monitoring is increasingly used to detect myocardial ischaemia. It is established that if patients on certain drugs and with normal resting electrocardiograms are excluded, ST segment depression correlates strongly with defects in myocardial perfusion.[15 16] A study in diabetic patients also found a good correlation between ST segment depression on ambulatory monitoring and positive exercise tests.[17] Our study shows that silent ischaemia is significantly more common in diabetic men with autonomic neuropathy than in those without. Furthermore, we identified a group of patients with autonomic neuropathy in whom silent ischaemia was the only manifestation of coronary artery disease. We did not attempt to define the extent of coronary artery disease by arteriography in these patients and even though it would be interesting to do so we do not consider it clinically justifiable at the present time.

The increased incidence of sudden death in patients with diabetic autonomic neuropathy may well be related to their relative inability to perceive warning anginal pain. We have shown that silent ischaemia is common in such patients. Our observations provide an important initial data base against which the subsequent course of the expanding study population can be examined. This will permit the eventual outcome to be compared with the presence or absence of autonomic neuropathy and give important information on any association that may exist between silent ischaemia and subsequent mortality.

1 Ewing DJ, Cambell IW, Clarke BF Mortality in diabetic autonomic neuropathy. *Lancet* 1976,i·601-3.

2 Ewing DJ, Cambell IW, Clarke BF Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications *Ann Intern Med* 1980;92 308-11

3 McB Page M, Watkins PJ. Cardiorespiratory arrest and diabetic autonomic neuropathy *Lancet* 1978;i·14-6

4 Niakan A, Harati Y, Rolak L, Comstock A, Rokey R. Silent myocardial infarction and diabetic autonomic neuropathy. *Ann Intern Med* 1986;146.2229-30

5 Barry J, Nabel E, Rocco MB, Campbell S, Selwyn AP Validation of a device for ambulatory monitoring and on line analysis of ischaemia in patients with angina [abstract] *J Am Coll Cardiol* 1986,7(suppl A)·239A

6 Garrett JS, Botvinich EH, Parmley WW, *et al* Reliable assessment of myocardial ischaemia with a new EKG monitor [abstract] *Clin Res* 1986,34:302A

7 Cary NC *SAS user's guide Statistics, version 5 edition* SAS Institute, 1985:418

8 Ewing DJ, Clarke BF Diagnosis and management of diabetic autonomic neuropathy *BMJ* 1982;285 916-8

9 Bellavere F, Bosello G, Fedele D, Cardone C, Ferri M Diagnosis and management of diabetic autonomic neuropathy [letter] *BMJ* 1983;287·61

10 Hilsted J, Jensen S. A simple test for autonomic neuropathy in juvenile diabetes *Acta Med Scand* 1979;205 385-7

11 Ewing DJ, Cambell IW, Murray A, Neilson JM, Clarke BF. Immediate heart rate response to standing simple test for autonomic neuropathy in diabetes. *BMJ* 1978,i 145-7

12 Faerman I, Faccio E, Milei J, *et al* Autonomic neuropathy and painless myocardial infarction in diabetic patients. histological evidence of their relationship *Diabetes* 1977,26.1147-58

13 Erikssen J, Thaulow E. Follow up of patients with asymptomatic myocardial ischaemia ' In Rutishauser W, Roskamm H, eds. *Silent myocardial ischaemia* Berlin. Springer-Verlag, 1984·154-64

14 Erikssen J. Prognostic importance of silent ischaemia during long term follow up of patients with coronary artery disease *Herz* 1987,12:359-68

15 Deanfield JE, Selwyn AP, Chierchia S, Maseri A, Ribeiro P, Krikler S. Myocardial ischaemia during daily life in patients with stable angina its relation to symptoms and heart rate changes *Lancet* 1983,i 753-8.

16 Deanfield JE, Shea M, Ribeiro P, *et al* Transient ST-segment depression as a marker of myocardial ischaemia during daily life *Am J Cardiol* 1984;54 1195-200

17 Chiarello M, Indolfi C, Cotecchia M, Sifola C, Romano M, Condorelli M Asymptomatic transient ST changes during ambulatory ECG monitoring in diabetic patients. *Am Heart J* 1985,110·529-34.

Br Heart J 1991;**66**:316–9

Myocardial ischaemia and ventricular arrhythmias precipitated by physiological concentrations of adrenaline in patients with coronary heart disease

Alastair J McCance, J Colin Forfar

Abstract

The clinical and haemodynamic effects of adrenaline infusion (30 ng kg^{-1} min^{-1}) producing plasma adrenaline concentrations in the range seen during acute myocardial infarction and of placebo were investigated in a crossover design in 14 patients with stable coronary heart disease. Adrenaline infusion resulted in electrocardiographic evidence of myocardial ischaemia (≥1 mm (0·1 mV) horizontal or downsloping ST segment depression) in 10 patients and angina in four, although the mean (SEM) increase in heart rate was modest (14 (2) beats/min) and mean coronary vascular resistance fell from 1·56 (0·21) to 1·16 (0·14) mm Hg min ml^{-1} ($p < 0·005$). New or increasingly frequent or complex ventricular arrhythmias occurred in five patients. Placebo infusion had no effect on the variables measured. Supine bicycle exercise during infusion of the saline placebo was associated with a similar degree of ST segment depression (0·9 (0·2) mm) as adrenaline infusion at rest (0·9 (0·1) mm) but exercise performed during adrenaline infusion (10 patients) resulted in more pronounced ST segment depression (1·9 (0·3) mm) ($p < 0·005$) than either intervention alone. Angina occurred in three of 11 patients during control exercise and in six of 10 during the combination of adrenaline infusion and exercise.

Such potentially adverse consequences of low dose adrenaline infusion in patients with stable coronary heart disease are consistent with the suggestion that adrenal activation is detrimental during acute myocardial infarction, being both arrhythmogenic and pro-ischaemic.

Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford
A J McCance
J C Forfar

Correspondence to
Dr Alastair J McCance,
Department of Cardiology,
Groby Road Hospital,
Leicester LE3 9QE.

Accepted for publication
23 May 1991

Acute myocardial infarction is associated with sympathoadrenal activation, and plasma adrenaline concentrations can reach 100 times the baseline upper limit of normal.[1] Karlsberg *et al* found that a high peak adrenaline concentration was associated with increased subsequent mortality,[1] but it is not clear whether this adverse outcome is due to the high adrenaline concentrations or whether high concentrations are a marker for large infarcts and associated with a poor prognosis for that reason. Nevertheless, the concept that adrenal activation may have significantly adverse consequences after acute myocardial infarction has received little recent attention. The aim of the present study was to investigate whether brief low dose adrenaline infusions, designed to simulate the increases in adrenaline concentration seen during acute myocardial infarction, result in myocardial ischaemia or ventricular arrhythmias in patients with stable symptomatic coronary heart disease.

Patients and methods

PATIENTS

Fourteen male patients, whose clinical details are shown in the table, were studied supine and in the fasting state one hour after diagnostic cardiac catheterisation. All had coronary heart disease (> 50% diameter stenosis of at least one major coronary artery), all had a history of stable typical angina, and six had had a previous myocardial infarction. Thirteen had had a diagnostic treadmill exercise test (Bruce protocol) at least one week before catheterisation. Chronic oral medication was stopped the day before study and β adrenoceptor antagonists were stopped at least 72 hours before. The resting left ventricular ejection fraction was determined from the right anterior oblique cineangiogram.[2] All subjects gave informed consent to the study, which was approved by the Central Oxford Research Ethics Committee.

METHODS

After left ventricular and coronary angiography, performed by the standard femoral approach, a Baim coronary sinus flow catheter (Electro-catheter Corporation, New Jersey) was inserted via the right subclavian vein. Correct placement in the distal coronary sinus was confirmed by injection of a small quantity of contrast material. This permitted repeated measurement of coronary sinus blood flow by thermodilution, as we have previously described.[3]

After insertion of the Baim catheter, patients were transferred to the research laboratory. Adrenaline (250 μg) was diluted to 50 ml in saline (154 mmol/l NaCl). Adrenaline (30 ng kg^{-1} min^{-1}) and matching saline placebo were infused double blind and in

Clinical data on 14 study patients with coronary heart disease

Case	Age (y)	LVEF (%)	BP (mm Hg)	CAD	Drugs	Diagnostic ETT (Bruce stage/degree and site of ST)
1	55	47	135/87	LAD, Cx, RCA	At, asp, nif, ISDN, ranit	2/none
2	40	55	157/92	Cx	At, asp, ISDN	2/2·5 mm/lat
3	64	75	141/78	LAD, Cx, RCA	At, asp, dilt, ISDN	2/2 mm/ant-lat
4	58	59	171/90	RCA	At, dilt, ISDN	2/none
5	58	68	190/101	LAD, Cx	At, asp, dilt, ISDN	2/1 mm/inf-lat
6	61	83	160/90	LM, LAD, Cx, RCA	At, asp, ISDN	4/1 mm/lat
7	46	58	108/63	RCA	At, asp, cimetidine	3/1 mm/lat
8	58	79	149/93	LAD, Cx, RCA	At, GTN	—
9	59	74	137/77	Cx	At, asp	3/1 mm/lat
10	67	62	164/94	RCA	At, asp	2/0·5 mm/lat
11	55	61	137/82	LAD, Cx	Tim, asp, nif, ISDN	2/1·5 mm/inf-lat
12	50	78	132/92	LAD, Cx, RCA	Met, asp, bezafibrate	2/3 mm/lat
13	44	64	105/73	Cx	At, asp	2/none
14	61	63	172/101	Cx, RCA	Bisop, asp, ISDN	2/2·5 mm/lat
Mean (SEM)	55 (2)	66 (3)	147/87 (6/3)			

Ant-lat, anterolateral; Asp, aspirin, at, atenolol; bisop, bisoprolol; BP, blood pressure; CAD, coronary artery disease; Cx, circumflex coronary artery; dilt, diltiazem; ETT, exercise tolerance test; GTN, long acting glyceryl trinitrate; inf-lat, inferolateral; ISDN, isosorbide dinitrate; LAD, left anterior descending coronary artery; lat, lateral; LM, left main coronary artery; LVEF, left ventricular ejection fraction; met, metoprolol; nif, nifedipine; ranit, ranitidine; RCA, right coronary artery; ST, ST segment depression; tim, timolol.

random order into a peripheral vein, each for 30 minutes. Eleven patients performed supine bicycle exercise using the left leg during the final 10 minutes of the first infusion. During the first minute of exercise the load on an electrically braked bicycle (Elema-Schönander AM 368, Sweden) was adjusted to a comfortable level and exercise was continued for 10 minutes. Exercise and the first infusion were then stopped and the patients rested supine for 10 minutes before the second infusion was started. Ten subjects repeated an identical exercise protocol during the final 10 minutes of the second infusion. Coronary sinus blood flow was measured in duplicate and standard 12 lead electrocardiograms were recorded at rest and during exercise during each infusion. The arterial blood pressure was measured every three minutes during the protocol by an automatic blood pressure recorder (Copal Digital Sphygmomanometer, UA 251) and three electrocardiographic leads were monitored continuously and recorded on magnetic tape. Adrenaline concentrations were measured by high performance liquid chromatography with electrochemical detection, as we have previously described.[4]

STATISTICAL ANALYSIS

The responses of the ST segment, blood pressure, heart rate, and rate-pressure product to exercise during saline and adrenaline infusion were compared by two way analysis of variance. Coronary vascular resistance and coronary blood flow during saline and adrenaline infusion were compared by a two tailed paired *t* test. All results are expressed as mean (SEM). Results were taken to be statistically significant at the 5% level.

Results

Adrenaline infusion increased the heart rate (81 (2) *v* 67(3) beats/min, $p < 0{\cdot}001$) and tended to increase systolic blood pressure (146 (6) mm Hg *v* 141 (7), $p < 0{\cdot}15$) and to decrease diastolic blood pressure (79 (4) *v* 82 (3) mm Hg, $p < 0{\cdot}1$). Adrenaline had no effect on mean arterial pressure (100 (4) *v* 102 (4) mm Hg). Coronary sinus blood flow increased during adrenaline infusion (109 (18) *v* 90 (18) ml/min ($p < 0{\cdot}001$) and there was a corresponding fall in coronary vascular resistance (1·16 (0·14) *v* 1·56 (0·21) mm Hg min/ml, $p < 0{\cdot}005$) (fig 1). There was no significant difference in any of the measured variables between infusion 1 and infusion 2 and thus no evidence of an order effect of the adrenaline and saline infusions. The mean exercise load achieved by the 11 patients who exercised was 26 (3) W.

During adrenaline infusion arterial and venous adrenaline concentrations increased from 0·37 (0·05) nmol/l to 3·09 (0·24) nmol/l ($p < 0{\cdot}001$) and from 0·31 (0·04) nmol/l to 1·64 (0·19) nmol/l respectively ($p < 0{\cdot}001$). No patient had significant ST segment depression at rest or during saline infusion. Ten of the 14 patients developed clear electrocardiographic evidence of myocardial ischaemia (≥ 1 mm (0·1 mV) horizontal or downsloping ST segment depression 80 ms after the J point) during adrenaline infusion, which was symptomatic in four, and one patient developed asymptomatic ST segment depression of <1 mm. Supine bicycle exercise resulted in electrocardiographic evidence of ischaemia in seven of 11 patients during saline infusion and ST segment depression of <1 mm in one patient. Angina developed during exercise in four patients. The degree of ST segment depression was similar at rest during adrenaline infusion and during the control exercise period (0·9 (0·1) mm and 0·9 (0·2) mm respectively). Exercise during the adrenaline infusion was associated with $\geq$ 1mm of ST segment depression in eight of 10 patients, and with angina in seven of these. The degree of ST segment depression (1·8 (0·3) mm) was significantly greater than during the control exercise period ($p < 0{\cdot}005$) (fig 2). Figure 3 shows representative electrocardiograms from a patient (case 6).

Exercise produced a greater increase in heart rate than adrenaline infusion (22 (3) beats/min *v* 14 (2) beats/min, $p < 0{\cdot}01$) and the increases in heart rate were similar during the control

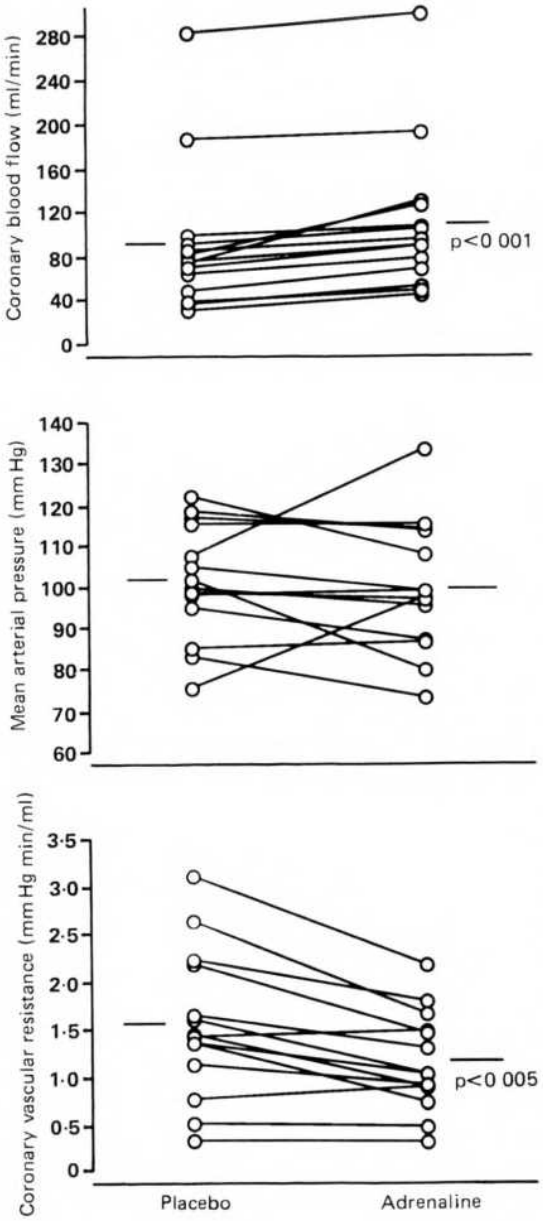


Figure 1 Thermodilution coronary sinus blood flow, mean arterial pressure, and calculated coronary vascular resistance during saline and adrenaline infusion (30 ng kg^{-1} min^{-1}) in 14 patients with coronary heart disease.

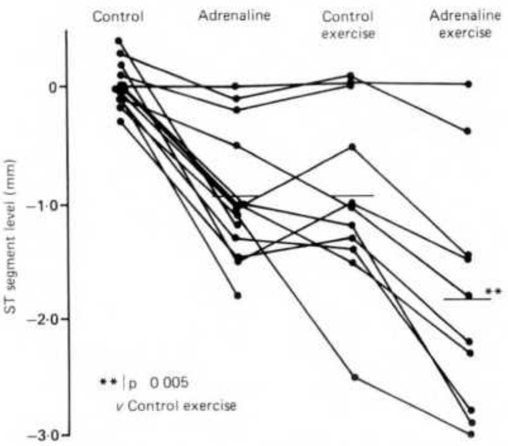


Figure 2 ST segment changes during adrenaline infusion, supine bicycle exercise during placebo infusion, and supine bicycle exercise during adrenaline infusion (1 mm = 0·1 mV). There was significant ST segment depression during both adrenaline infusion and control exercise in most patients and the degree of ST segment depression was greatest during the adrenaline exercise period.

and adrenaline exercise periods (22 (3) beats/min v 20 (3) beats/min). The rate-pressure product (9493 (811) mm Hg. beats min^{-1} at rest during placebo) increased during adrenaline infusion and during both exercise periods, but was greater during the control exercise period (13857 (1784) mm Hg. beats min^{-1}) than during adrenaline infusion at rest (11924 (671) mm Hg. beats min, $p < 0{\cdot}01$) and was greatest during adrenaline infusion and exercise (16801 (1100) mm Hg. beats min^{-1}, $p < 0{\cdot}01$ *v* exercise placebo and rest adrenaline).

Ventricular arrhythmias occurred for the first time, or, if already present, became more frequent or more complex in five of 14 patients during adrenaline infusion. Two patients developed unifocal ventricular extrasystoles during the adrenaline exercise period, when none had been present at rest or during the control exercise period. One patient, who did not exercise, developed ventricular couplets during adrenaline infusion, infrequent multifocal ventricular extrasystoles having been present during the saline infusion; one patient developed frequent ventricular extrasystoles, a brief period of ventricular bigeminy, and ventricular couplets during both control and adrenaline exercise periods; and one patient developed sustained ventricular bigeminy during adrenaline infusion, having had no arrhythmia at rest or during the control exercise period. No arrhythmia required specific treatment.

Discussion

In this study of patients with one, two, three, and four vessel coronary heart disease, infusion of adrenaline to produce physiological increases in plasma adrenaline concentration frequently resulted in myocardial ischaemia, which was often asymptomatic. Ventricular arrhythmias were also frequently precipitated

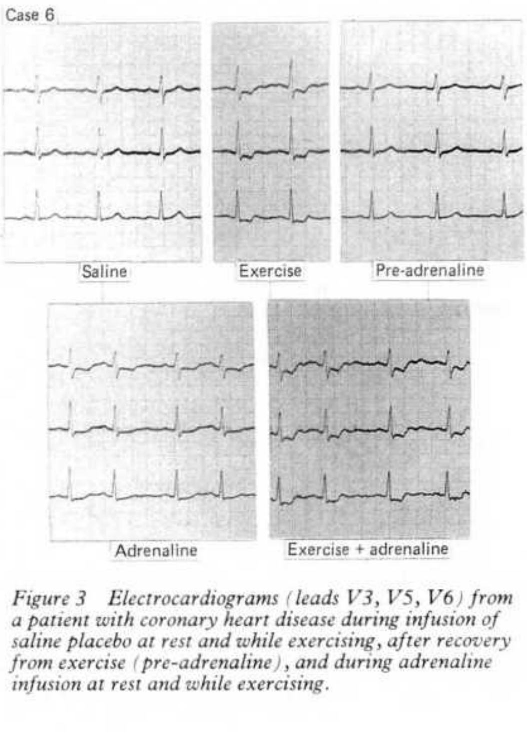


Figure 3 Electrocardiograms (leads V3, V5, V6) from a patient with coronary heart disease during infusion of saline placebo at rest and while exercising, after recovery from exercise (pre-adrenaline), and during adrenaline infusion at rest and while exercising.

or exacerbated. The concentrations of adrenaline in this study, 1·64 (0·19) nmol/l and 3·09 (0·24) nmol/l in venous and arterial plasma respectively, are well within the range reported in patients with acute myocardial infarction. McAlpine *et al* reported admission venous adrenaline to be 3·54 (1·30) nmol/l in patients with acute myocardial infarction and heart failure,[5] while in patients with cardiogenic shock Benedict and Grahame-Smith reported a mean (SE) adrenaline concentration of 6·17 (1·04) nmol/l[6] and Karlsberg *et al* reported values as high as 37·7 nmol/l.[1] The concentrations of adrenaline produced in this study are also reached during heavy physical exercise, when mean venous adrenaline concentrations of 2·0–3·5 nmol/l have been reported.[7,8] In normal healthy controls these concentrations of adrenaline, whether the result of adrenaline infusion or exercise, are well tolerated,[9,10] but this is not the case in patients with coronary heart disease. The dose of adrenaline used in this study is approximately 30 times less than the dose used in anaphylactic shock or cardiac arrest.

The potential adverse effects of adrenaline in the setting of acute myocardial infarction are well recognised: the positive inotropic and chronotropic effects of β adrenoceptor stimulation may compromise oxygen balance in critically underperfused myocardium, thus increasing infarct size[11] and possibly the risk of myocardial rupture, and may cause distant myocardial ischaemia in patients with multivessel coronary disease (further compromising pump function and increasing the risk of arrhythmia): the direct arrhythmogenic effects and potential cardiotoxicity of catecholamines are well known.[12,13] Also of potential importance in view of the advent of thrombolytic therapy is the suggestion that catecholamines may be implicated in the genesis of reperfusion arrhythmias.[14]

We cannot be certain whether the deleterious effects of adrenaline are catecholamine specific or are due to the increase in heart rate, but it seems unlikely that it is purely a heart rate effect. Adrenaline infusion caused myocardial ischaemia as severe as did supine bicycle exercise, although the heart rate and rate-pressure product were less during adrenaline infusion than during supine bicycle exercise. Although increased oxygen demand, of which the rate-pressure product is an indicator,[15,16] was clearly a factor in producing ischaemia during adrenaline infusion, the lesser double product for a similar degree of ischaemia compared with dynamic exercise suggests that other mechanisms may also have been operating. One possibility is local coronary steal. It has been suggested that α mediated coronary vasoconstriction may help to maintain subendocardial flow during exercise.[17] Humoral adrenaline, a potent β_2 as well as an α agonist, is likely to have been less active in this regard than neuronally secreted noradrenaline, and although coronary blood flow increased and total coronary vascular resistance fell during adrenaline infusion it is possible that coronary vasodilatation in normal segments, especially those distal to an organic stenosis, may have diverted flow away from the ischaemic subendocardium.

We showed that in patients with stable, symptomatic coronary heart disease infusion of low dose adrenaline to mimic the increases in adrenaline concentration seen during acute myocardial infarction commonly caused myocardial ischaemia and ventricular arrhythmias. Although the situation in acute myocardial infarction is manifestly not the same as in chronic stable ischaemic heart disease it is likely that adrenaline has similar and potentially important deleterious effects in acute infarction. The current study raises the possibility that adrenaline, in addition to having a direct arrhythmogenic effect, may promote ischaemia distant from the area of infarction without causing substantial changes in heart rate or blood pressure.

This work was supported by the British Heart Foundation AJM was a Syntex research fellow. We acknowledge the expert technical assistance of Mr PA Thompson

1 Karlsberg RP, Cryer PE, Roberts R Serial plasma catecholamine response early in the course of acute myocardial infarction. relationship to infarct extent and mortality. *Am Heart J* 1981,102 24-9.

2 Sandler H, Dodge HT. Angiographic methods for determination of left ventricular geometry and volume. In Mirsky I, Ghista GN, Sandler H, eds *Cardiac mechanics physiological, clinical and mathematical considerations* New York John Wiley, 1974 141

3 McCance AJ, Forfar JC. Cardiac and whole body [^{3}H]noradrenaline kinetics in ischaemic heart disease. contrast between unstable anginal syndromes and pacing induced ischaemia *Br Heart J* 1989,61.238–47.

4 McCance AJ, Forfar JC Cardiac and whole body [^{3}H]noradrenaline kinetics during adrenaline infusion in man *Clin Sci* 1991;80 227–33.

5 McAlpine HM, Morton JJ, Leckie B, Rumley A, Gillen G, Dargie HJ. Neuroendocrine activation after acute myocardial infarction. *Br Heart J* 1988,60.117-24

6 Benedict CR, Grahame-Smith DG. Plasma adrenaline and noradrenaline concentrations and dopamine-β-hydroxylase activity in myocardial infarction with and without cardiogenic shock *Br Heart J* 1979,42.214-20

7 Cryer PE. The physiology and pathophysiology of the human sympathoadrenal neuroendocrine system *N Engl J Med* 1980,303·436–44.

8 Halter JB, Stratton JR, Pfeifer MA. Plasma catecholamines and haemodynamic responses to stress states in man. *Acta Physiol Scand* 1984;527(suppl) 31-8

9 Fellows IW, MacDonald IA, Bennet T, O'Donoghue DP Effect of intravenous infusion of adrenaline on the cardiovascular responses to distal subatmospheric pressure in man *Clin Sci* 1988,75·389-94

10 Freyschuss U, Hjemdahl P, Juhlin-Dannfelt A, Linde B Cardiovascular and metabolic responses to low dose adrenaline infusion. an invasive study in humans *Clin Sci* 1986,70:199-206

11 Herbaczynska-Cedro K. The influence of adrenaline secretion on the enzymes in heart muscle after acute coronary occlusion in dogs. *Cardiovasc Res* 1970;4.168-75.

12 Corr PB, Witkowski FX, Sobel BE Mechanisms contributing to malignant dysrhythmias induced by ischemia in the cat. *J Clin Invest* 1978;61 109-19

13 Rona G Catecholamine cardiotoxicity *J Mol Cell Cardiol* 1985,17:291-306

14 Schwartz PJ, Zuanetti G Role of the autonomic nervous system in reperfusion arrhythmias *J Mol Cell Cardiol* 1988;20(suppl II) 113–8

15 Armbrecht JJ, Buxton DB, Brunken RC, Phelps ME, Schelbert HR Regional myocardial oxygen consumption determined noninvasively in humans with 1-[^{11}C]acetate and dynamic positron tomography *Circulation* 1989, 80 863-72.

16 Camici P, Marraccini P, Marzilli M, *et al*. Coronary hemodynamics and myocardial metabolism during and after pacing stress in normal humans. *Am J Physiol* 1989,257:E309-17.

17 Feigl EO The paradox of adrenergic coronary vasoconstriction. *Circulation* 1987,76.737–45.

Br Heart J 1991;66:320-1

CASE REPORT

Paradoxical embolisation of a catheter fragment to a coronary artery in an infant with congenital heart disease

Howard S Klys, Anthony P Salmon, Joseph V De Giovanni

Abstract

Six weeks after cardiac catheterisation via the right femoral vein an infant underwent an anatomical correction for transposition of the great vessels and closure of a large ventricular septal defect. The patient died intraoperatively as a result of severe left ventricular dysfunction. Necropsy showed an old myocardial infarction associated with thrombosis of the circumflex coronary artery. Electron probe *x* ray analysis showed that foreign refractile material within the thrombus contained bismuth, an element used in the construction of some cardiac catheters. This is believed to be the first report of "paradoxical" coronary embolisation of catheter-derived material and highlights the usefulness of electron probe *x* ray analysis.

Case report

A six week old infant presented to Birmingham Children's Hospital with a three week history of poor feeding and failure to thrive. On examination he was cyanosed and in heart failure. Echocardiography showed situs solitus, atrioventricular concordance, ventriculoarterial discordance (complete transposition of the great arteries), and a large perimembranous ventricular septal defect. Left ventricular fractional shortening was 35% (normal range 25–42%) with uniform function. At cardiac catheterisation a small patent foramen ovale was found but could not be crossed with a septostomy catheter. However, after a guide wire was passed across the foramen it was possible to cross the septum with a Mullins's sheath. A blade septostomy was performed with a Park Blade and this was followed by a balloon atrial septostomy. The left atrial pressure fell from a mean of 20 mm Hg to 11 mm Hg and the right atrial oxygen saturation rose from 43% to 79%. The aorta was not entered. The patient remained stable throughout the procedure.

The next day he appeared pale and sweaty and became pyrexial. Echocardiography showed an adequate septostomy but the left ventricular function was impaired (fractional shortening 22%). The electrocardiogram showed ST segment depression and T wave inversion in all leads. A clinical diagnosis of sepsis was made and he was treated with antibiotics. His condition rapidly improved and he was discharged within a week.

Three weeks later he was admitted with a febrile illness associated with lymphocytosis. Viral studies were negative and over the subsequent three weeks his temperature resolved. A repeat echocardiogram showed that left ventricular size and fractional shortening (36%) had returned to normal. Six weeks after catheterisation he underwent an arterial switch repair with closure of the ventricular septal defect. The operation was technically successful but it was impossible to discontinue cardiopulmonary bypass because of severe left ventricular dysfunction. The patient died.

At necropsy, sectioning of the left ventricle showed a transmural fibrous scar, 2·5 cm across, in the apical portion of the posterior wall. The anastomotic lines of the great vessels were intact and the coronary ostia were patent. The coronary artery anatomy was type D according to the Yacoub classification of transposition of the great arteries—that is, the right coronary artery and the circumflex coronary artery arose from the right posterior sinus and the left anterior descending coronary artery from the left posterior sinus. Examination under a dissecting microscope showed that a 1·5 cm length of the circumflex artery was occluded where it lay in the atrioventricular sulcus. Histological examination of the posterior wall of the left ventricle confirmed an infarct that was several weeks old. There was no evidence of myocarditis. Organised thrombus with partial recanalisation was found within the circumflex artery (fig 1A). Higher power magnification showed giant cells containing refractile foreign material within the thrombus (fig 1B). This material was analysed by electron probe *x* ray analysis[1]: paraffin sections of the circumflex artery were examined in a Joel 100 CX electron microscope in the back-scatter mode. Analysis by energy dispersive *x* ray analysis (Link Systems) showed the presence of both iron and bismuth (fig 2).

Discussion

The day after cardiac catheterisation the infant was unwell and in retrospect it became clear that he had sustained a myocardial infarction during the procedure. In transposition of the great arteries extensive infarction of the left

Department of Pathology, The Children's Hospital, Birmingham
H S Klys

The Heart Unit, The Children's Hospital, Birmingham
A P Salmon
J V De Giovanni

Correspondence to
Dr Joseph V De Giovanni,
The Heart Unit, The
Children's Hospital,
Ladywood Middleway,
Birmingham B16 8ET.

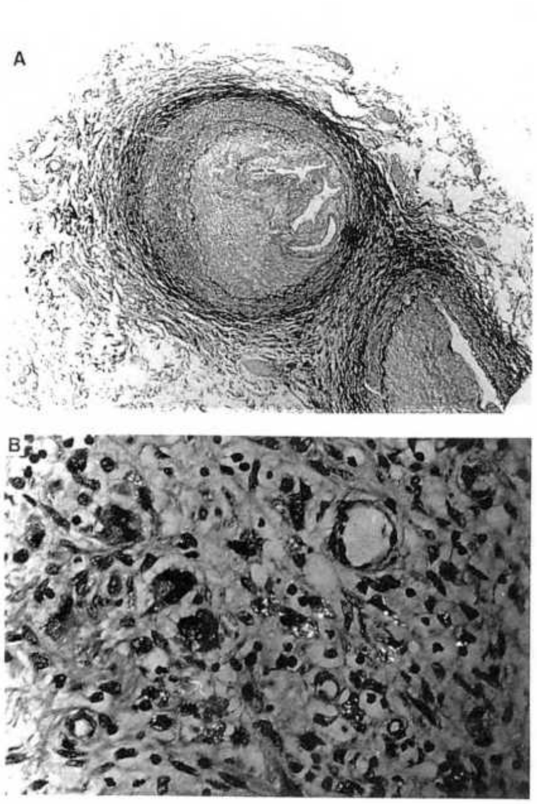


Figure 1 (A) An organised and recanalised thrombus in the circumflex artery (elastic van Gieson, original magnification was × 48). (B) Giant cells within the thrombus containing particles of refractile material (haematoxylin and eosin, original magnification was × 480).

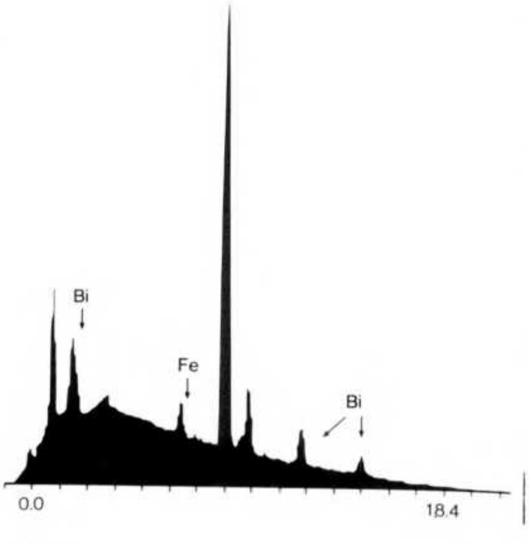


Figure 2 Electron probe x ray analysis of the refractile material within the thrombus showed an excess of bismuth (catheter derived) and iron (haemosiderin).

ventricle may not prove fatal because this ventricle supplies the low resistance pulmonary circulation. In transposition of the great arteries with a ventricular septal defect left ventricular preload is increased and afterload reduced. The apparent return to normal left ventricular function (fractional shortening 36%) was misleading and the inevitable increase in afterload that occurred after anatomical correction resulted in intractable cardiac failure. If the degree of left ventricular dysfunction had been recognised we would have opted for an inflow correction, leaving the right ventricle as the systemic chamber.

Electron probe *x* ray analysis is a method of in situ elemental analysis that has the unique ability to relate chemical composition to tissue morphology. The technique combines high sensitivity (as little as 10^{-19}g of an element will be detected) with near total specificity. The refractile material found in the lumen of the occluded circumflex coronary artery contained bismuth salts, which are frequently used to make catheters radio-opaque.

The pathological findings and clinical history provide conclusive evidence that coronary artery thrombosis occurred at the time of cardiac catheterisation. No damage to the catheters was noted during the procedure and we assume that the fragment arose from within the lumen. Winding showed the large number of particles released when cardiac catheters are flushed and the increased risk after one insertion of a guide wire.[2] Other evidence also suggests an increased risk of fragment separation from re-used catheters.[3] In our case several guide wire insertions were performed during a technically difficult procedure. Clinically important paradoxical *coronary* embolisation is rare[4] and, to our knowledge, paradoxical coronary embolisation of catheter-derived material has not previously been reported. The present trend toward interventional catheterisation and the extensive use of guide wires highlights the continuing need for improved catheter technology.

We thank Dr F Raafat, consultant pathologist, for his assistance in preparing this paper, and Mr Tony Sims at the Electron Microscopy Unit of Leicester University for providing us with the information on electron probe *x* ray analysis.

1 Ghadially FN. The technique and scope of electron probe *x*-ray analysis in pathology. *Pathology* 1979;**11**:95-100.
2 Winding O. Particle release from angiographic utensils. *Eur J Radiol* 1981;**1**:140-2.
3 Kyriakides ZS, Bellenis IP, Caralis DG. Catheter separation duration cardiac catheterisation and coronary angiography. A report of four incidents and review of literature. *Angiology* 1986;**37**:762-5.
4 Jungbluth A, Erbel R, Darium H, Rumpelt H-J, Meyer J. Paradoxical coronary embolism: case report and review of the literature. *Am Heart J* 1988;**116**:879-85.

Br Heart J 1991;66:322-4

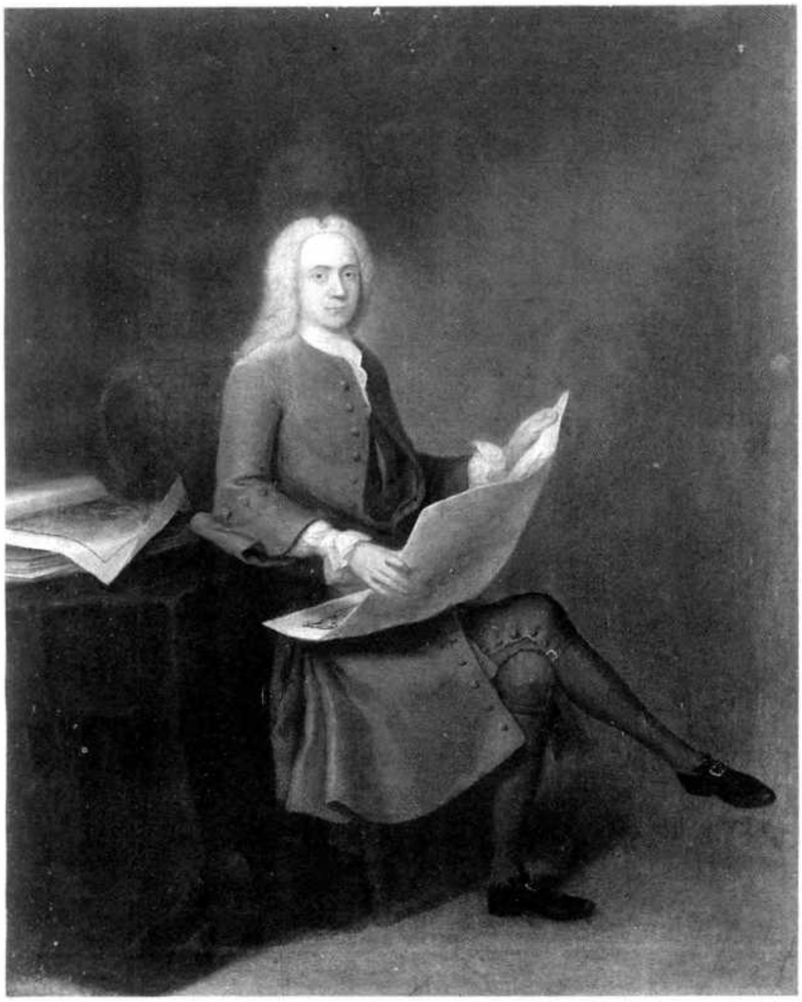
John Fothergill and angina pectoris

William L Proudfit

Correspondence to:
Dr William L Proudfit,
Cleveland Clinic
Foundation, One Clinic
Center, 9500 Euclid Avenue
Cleveland, Ohio 44195, USA

Accepted for publication
23 May 1991

William Heberden presented his original description of angina pectoris to the College of Physicians in London on 21 July 1768.[1] In it he said that he "consulted an able physician of long experience, who told me that he had known several ill of it, and that all of them had died suddenly." Although the latter phrase does not fit precisely the experience of John Fothergill, it is likely that he was the physician mentioned. Fothergill was a friend of Heberden, who supported his application to the College of Physicians.[2] Fothergill had recognised angina pectoris long before Heberden described and named it in his lecture.[3]



From an oil portrait of John Fothergill by an unknown artist, courtesy of the Royal College of Physicians.

General background

John Fothergill was born in Yorkshire in 1712, two years after Heberden.[4 5] He was the son of a prosperous Yorkshire farmer and preacher of the Quaker faith. Fothergill received his medical degree from the University of Edinburgh in 1736. Although he went to St Thomas's Hospital, London after graduation and stayed at least two years, it is not clear what he did between 1738 and 1740. It is probable that he made a start in private practice. He received a box of seeds packed by John Bartram, the famous self educated American Quaker naturalist, in September 1738, delivered by Dr Thomas Bond, a Philadelphia physician.[6] Possibly Bond met Fothergill in St Thomas's Hospital; and Bond, the same age as Fothergill, gave the seeds as a token of esteem. Bond returned to Philadelphia from Paris in the early 1740s and sang the praises of Fothergill to Bartram. Correspondence sprang up between Bartram and Fothergill and lasted the rest of Bartram's life. In 1740 Fothergill travelled to Belgium, Holland, and Germany with friends and started his real practice when he returned to London the same year. His practice flourished because of his professional ability and his free service to the poor, but remuneration was low initially. Gradually a larger number of affluent citizens consulted him and after his widely translated paper on sore throat (an original description of diphtheria, but some cases had scarlet fever) was published in 1748, he was famous and busy. In addition to medical practice, he did a great deal of medical and scientific writing and was a medical editor. He was active in medical societies and was interested in medical education. Fothergill was elected Fellow of the Royal Society in 1768.

Despite the pressure of a large practice, Fothergill continued to be concerned about the plight of the poor and often the monetary component of his medical care went from doctor to patient rather than the usual direction. In addition he was active in private philanthrophy and public causes. His societal interests included vital statistics, condition of prisons, police, internal commerce, public baths, cemeteries, abolition of slavery, and a Quaker school for children. Fothergill's father had visited America for evangelistic purposes and this may have influenced John in the development of many friendships in the colonies. Fothergill had extensive correspondence with his American friends and supported financially schools in Willamsburg, Philadelphia, and New York. He made large contributions to the University of Pennsylvania and the Pennsylvania Hospital. He was one of the earliest members of the American Philosophical Society. Fothergill was an active apologist for the American colonists and he and Benjamin Franklin, his friend and patient, carried out intense negotiations in an effort to prevent rupture of diplomatic relations. Fothergill remained supportive of Americans until his death in 1780.

Although Fothergill was famous in London and the American colonies for other reasons, he was most renowned in the mind of the British general public outside London and on the European continent as a horticulturalist. He was a botanist and he constructed extensive gardens and an enormous greenhouse that included the largest variety in all Europe, according to Sir Joseph Banks, the President of the Royal Society. Linnaeus named a plant Fothergilla after his friend, an appropriate designation for an American plant. Fothergill's gardens included many American plants and shrubs whose seeds, cuttings, or whole plants were sent by his friend John Bartram.[6] He and Bartram developed original techniques for transporting these specimens to London. Fothergill also had an extensive collection of shells and smaller but select accumulations of butterflies and minerals.

John Fothergill made significant medical contributions in addition to his description of diphtheria. He wrote an excellent account of "sick head-ach" (migraine). Trigeminal neuralgia was described first by Fothergill. The second part of his first paper on angina pectoris is an accurate description of two cases of what now is called Pickwickian syndrome. It is ironic that his name is not attached to any of his original descriptions.

Angina pectoris

If Fothergill was Heberden's "able physician of long experience" why was he not mentioned by name? A large botanical volume was dedicated to Fothergill, but he withdrew his initial approval before publication because he did not think himself worthy. It may be that this attitude was responsible for Heberden's omission, for Heberden was generous in his support of colleagues. Fothergill reported postmortem examinations of two of his patients who had been diagnosed as having angina pectoris. His two reports were published consecutively in 1776.[3 7] He stated that "the disease was of that kind which is so fully and judiciously described by Dr Heberden." It is evident that Fothergill gave an oral presentation of his first case to the Society of Physicians of London, but the date is not given. The patient died 14 May 1774 and Fothergill must have made his report late in 1774 or early 1775. He states in the second case report that death occurred on 13 March 1775 and that this date was after the first case report had been delivered.

Fothergill gave detailed case histories of the patients, both of whom died suddenly. In the first paper he mentioned the postmortem findings of another person who had experienced angina and anasarca. A "small ossification in one of the mitral valves" was found. Fothergill states that patients with angina usually had "an irregular and intermitting pulse" even when free from pain. This combination of observations led him to ask the prosectors in the first reported case "to attend to the condition of the heart with all possible accuracy." The prosectors were "the Langleys, two judicious surgeons in the neighbourhood". These appear to have been Arnold and Thomas Langley who practiced at Red Lion Square, London, at the time of compilation of the 1777 list of members of the Corporation of Surgeons, the earliest roll possessed by The Royal College of Surgeons of England (personal communication from I F Lyle, librarian). They found "near the apex, a small white spot as big as a sixpence, resembling a cicatrix." The coronary arteries were not mentioned in the necropsy report. Fothergill wondered whether the excessive amount of fat in the mediastinum, pericardium, and omentum might have been responsible for this patient's angina. Accordingly he went on to describe two morbidly obese, somnolent young people. A young man lost weight on a vegetable diet and regained his health and a young woman improved with weight loss, but relapsed with abandonment of her diet and died suddenly at age 27. At necropsy, nothing was found except for obesity. Lacking more specific treatment Fothergill advised a vegetable diet for patients who had angina.

In his first report Fothergill mentioned that he had seen a man about 30 years of age who had angina pectoris, the youngest victim he had observed. He had been consulted by the patient "above 20 years ago"—presumably before 1754, at least 14 years before Heberden's original report. This man showed gradual improvement and then disappearance of angina, the only case of complete "cure" of the condition in Fothergill's experience. He had observed others whose angina had lessened "but for the most part .... the prognostic is unfavourable."

In the second case, John Hunter, "that very skilful and accurate anatomist", was engaged to do the postmortem examination, which showed mitral and aortic valvular disease but apparently not very severe in extent. Calcifications were noted in the aorta. "The two coronary arteries, from their origin to many of their ramifications upon the heart, were become one piece of bone." Scars were found in the left ventricle. Despite the fact that Hunter had encountered coronary disease at necropsy in 1770, he apparently did not examine the coronary arteries of Heberden's case in May 1772.[8 9] Hunter himself had angina by 1773, so it is remarkable that his postmortem findings of Fothergill's patient in 1775 did not seem to impress him.[10] He said that "there was nothing very remarkable in his case worth taking notice of."[8] Fothergill, in giving the case history, wrote that "in a sudden and violent transport of anger, he fell down and expired immediately." The same fate in the same circumstances awaited John Hunter in 1793, and Hunter had anticipated its possible occurrence.[10]

In his discussion of this case, Fothergill said that "the state of the parts about the heart fully shew, that under such circumstances, it is impossible to bear with impunity the effects of sudden and violent agitations, whether they arise from gusts of passion, or suddenly accelerated muscular motion." He did not specify which of the cardiac abnormalities might be responsible for angina pectoris nor did he speculate on the possible mechanism.

Evaluation

It has been said that Fothergill was the first to ascribe angina pectoris to coronary artery disease. A more accurate statement is that he was one of the first to suspect the association of cardiac disease and angina pectoris. The date of Fothergill's original suspicion cannot be determined, but John Wall, in a letter to Heberden dated 30 May 1772, attributed angina pectoris to aortic stenosis demonstrated at necropsy. Heberden read Wall's report to the College of Physicians on 17 November 1772, although publication was delayed until 1785.[11] Certainly Fothergill did not emphasise the importance of coronary disease. It remained for Edward Jenner and Samuel Black independently to lay the foundation for the ischaemic theory of causation of angina.[12]

Fothergill died in December 1780 of prostatic obstruction probably due to carcinoma. Benjamin Franklin wrote to a physician friend, "I think that a worthier man never lived."[13]

1 Heberden W. Some account of a disorder of the breast *Medical Transactions, published by the College of Physicians in London* 1772;2:59–67.

2 Heberden E. *William Heberden: physician of the age of reason.* London: Royal Society of Medicine Services, 1989.

3 Fothergill J. Case of angina pectoris, with remarks. *Medical Observations and Inquiries by a Society of Physicians in London* 1776;5:233–51.

4 Lettson JC. *The works of John Fothergill.* Volume III. London. Charles Dillog, 1783.

5 MacMichael W. *Lives of British physicians.* London: Murray, 1830

6 Berkeley E, Berkeley DS. *The life and travels of John Bartram.* Tallahassee· Florida State University Book, 1982.

7 Fothergill J. Farther account of the angina pectoris. *Medical Observations and Inquiries by a Society of Physicians in London* 1776;5:252–8.

8 Hunter J Case Books, transcribed in five volumes by William Clift, 1826. Unpublished. Library of the Royal College of Surgeons of England.

9 Parry CH. *An inquiry into the symptoms and causes of the syncope anginosa, commonly called angina pectoris.* Bath: R Crotwell, 1799.

10 Hunter J. *A treatise on blood, inflammation and gun-shot wounds to which is prefixed a short account of the author's life by his brother-in-law Everard Home.* London: G Nichol, 1794.

11 Wall J. A letter from Dr Wall to Dr Heberden on the same subject (angina pectoris). *Medical Transactions, published by the College of Physicians in London* 1785,3:12–24

12 Proudfit WL. Origin of concept of ischaemic heart disease. *Br Heart J* 1983,50:209–12.

13 Garner BC, Booth CC. *Chain of friendship· letters of Dr Fothergill.* Cambridge: Harvard University Press, 1971.

Br Heart J 1991;66:325–31

BRITISH CARDIAC SOCIETY

Coronary angioplasty in the United Kingdom

Report of a working party of the British Cardiac Society

Members of working party:

Guy's Hospital, London
Edgar Sowton (chairman)

University of Leicester Glenfield General Hospital, Leicester
David de Bono

John Radcliffe Hospital, Oxford
Brian Gribbin

Belfast City Hospital, Belfast
Barry O'Keeffe

Walsgrave Hospital, Coventry
Man Fai Shui

Airdale General Hospital, Keighley, West Yorkshire
Paul Silverton

Correspondence to Dr Edgar Sowton, Guy's Hospital, St Thomas Street, London SE1 9RT.

Accepted for publication 26 March 1991

1 Introduction

1.1 BACKGROUND

Percutaneous transluminal coronary angioplasty (PTCA) was first performed by the late Dr Andreas Grüntzig in 1977[1] and patients have been treated in Britain for over ten years.

Successful PTCA restores blood flow to ischaemic heart muscle by temporary inflation of a balloon within a diseased segment of a coronary artery. After removal of the balloon the previously stenosed segment is left wide open but with a very disrupted surface. Subsequent healing can lead to establishment of a normal lumen but in a substantial minority a stenosis recurs usually within the first six months. The procedure is carried out under local anaesthesia. It is usually performed in a cardiothoracic centre and requires a skilled team and high quality catheter laboratory. Major advantages are the very short hospital stay (typically two to three days), the patient's ability to return to full activities immediately without prolonged convalescence, and the possibility of repeat procedures for future disease.

1.2 PURPOSE OF THIS REPORT

The aims of this report are to:

(i) Assess the need for PTCA in the United Kingdom.
(ii) Identify the facilities available.
(iii) Estimate the increase in demand.
(iv) Review the relation between cardiac bypass surgery and PTCA.
(v) Consider the implications for costs and training.

2 Indications for PTCA

Revascularisation on symptomatic or prognostic grounds should be indicated before PTCA is considered—as it is before coronary artery bypass grafting (CABG) is considered. The population of patients that can be treated by angioplasty overlaps partially, but not completely, with those who are suitable for CABG. Continuing changes in apparatus and skills are leading to rapid expansion of indications for PTCA. Even in 1987 over 50% of patients treated by PTCA in many centres in the United States had multivessel disease[2] and this trend has been followed in the United Kingdom. The main patient groups in which PTCA should be considered are discussed below. These groups are not mutually exclusive. The procedure can be carried out in elderly patients (over the age of 80), though the risks are higher.[3]

2.1 PATIENTS WITH STABLE ANGINA

PTCA may be the appropriate treatment when stenoses in one or more coronary arteries are discrete, short, proximal enough to be reached by the balloon catheter, and preferably not in the immediate vicinity of acute bends or large side branches. Bifurcation stenoses can be dealt with by two wire "kissing balloons" or by double fixed wire techniques.[4 5] Total or subtotal occlusions may also be re-opened by PTCA in many cases. Favourable factors include the presence of a proximal stump in which to engage the balloon, a relatively short duration of occlusion (three months or less), and good visualisation of the distal vessel from retrograde filling. New technology for disobliteration of occluded arteries is being introduced with increasing frequency.[6]

2.2 PATIENTS WITH UNSTABLE ANGINA

Most reported series include a high proportion of patients with unstable angina and similar success rates are achieved as when angina is stable. The acute situation was usually controlled with bed rest and nitrates before the PTCA was performed. Emergency PTCA is available as a method to reverse continuing deterioration when medical treatment fails to produce improvement, but the risks are somewhat higher than when the patient's condition is stabilised.[7]

2.3 PATIENTS DURING MYOCARDIAL INFARCTION

Attempts have been made to reverse myocardial infarction by emergency PTCA of an occluded coronary artery.[8] Although some success has been reported the technique is only applicable where patients can be transferred to a catheterisation laboratory at a very early stage. At the present time in the United Kingdom this restricts the approach to patients who develop infarction while in hospital or who can be transferred urgently from the immediate surroundings. It also requires that a catheterisation laboratory and an angioplasty team are available immediately. With the advent of thrombolysis as the immediate treatment for myocardial infarction the indications for emergency PTCA have diminished.[9]

2.4 PATIENTS WITH PREVIOUS BYPASS GRAFTS

Many patients whose CABG operations were performed some years ago are again developing angina, either from graft stenosis or from progression of the native disease. Repeat CABG is often unnecessary because many such patients can be treated by angioplasty, though high rates of restenosis have been reported particularly in late graft failure.[10] In several centres in the United States 20–25% of angioplasty patients have undergone previous bypass graft surgery. The proportion in the United Kingdom is lower than this but is steadily increasing.

In addition to dilatation of stenoses in the body of the bypass graft, lesions at the attachment of the graft to the aorta or to the insertion into the distal vessel may be dilated. Additional use can be made of the graft as a conduit by which a balloon can be passed to the distal native vessel for the treatment of otherwise unapproachable lesions.[11]

2.5 PATIENTS IN WHOM CABG IS INAPPROPRIATE

A small group of patients with severe angina may be considered for angioplasty even though a bypass graft operation is not advisable. The group includes patients in whom the prognosis is poor because of other diseases, such as malignancy, renal failure etc, and those whose operative risk is judged unacceptably high because of concomitant lung disease, previous strokes, or extremely poor left ventricular function. In such patients a palliative "salvage angioplasty" may produce relief from angina for the remaining lifetime of the patient.[12]

3 Present results of PTCA

3.1 IMMEDIATE RESULTS

In experienced hands the initial procedure has a success rate in excess of 90% for dilatation of a single stenosis, 75%–80% for re-opening a near total stenosis, and 50%–70% for disobliteration of a chronic total occlusion. Usually it fails because the lesion cannot be crossed with the guidewire or the balloon. Complications include precipitation of myocardial infarction, major coronary artery dissection, and abrupt closure of the artery requiring immediate bypass surgery. Mortality varies with myocardial function and complexity of the procedure but should be much less than 1%.

The need for immediate bypass surgery is considered later in this report.

3.2 SHORT TERM RESULTS

The most important factor is the recurrence rate which varies in different reports from 20% to almost 50%. Currently recurrence of angina within one month is regarded as being due to inadequate dilatation while return of angina between one and six months is likely to be due to recurrence of the stenosis during the healing phase. Both groups form a population requiring further assessment. About half will be treated with further angioplasty with a high degree of success. This procedure can be repeated several times.[13]

The likelihood of restenosis differs between vessels, being highest in the left anterior descending coronary artery and lowest in the circumflex coronary artery.[14] It is higher:

(i) when the dilated lesion was near the origin of an artery than when it was distal,
(ii) when a totally occluded artery has been reopened,
(iii) in a graft than in a native vessel.

It is not established that the incidence of restenosis is reduced by the use of new techniques such as atherectomy or stenting.

When angina develops more than one year after the procedure it is usually caused by progression of the native disease and in this respect PTCA patients do not differ from those undergoing CABG.

3.3 LONG TERM RESULTS

Follow up on large numbers of patients is available for relatively few years but some patients in the United Kingdom remain free from symptoms 10 years after angioplasty. Over 80% of patients who have angioplasty are free from pain five years later.[15]

4 Activity levels in the United Kingdom

4.1 SOURCE OF DATA

Reports of the total number of patients treated by PTCA as an initial procedure were requested from all known angioplasty centres in the United Kingdom, including private hospitals. A postal questionnaire was addressed to all cardiologists and radiologists in each unit known to be performing procedures and the returns were compared. Where no information was received a telephone follow up was instituted.

Direct inquiries were also made to the nursing sister in charge of the procedure room, usually the catheterisation laboratory. We are grateful for the effort expended by these nurses in counting back through the record books to supply figures of the number of coronary angioplasties performed each year.

We asked the information office at each district health authority in the United Kingdom for information on the number of PTCA procedures, and particularly the number of new patients, being dealt with within their district year by year.

Commercial agents and distributors of angioplasty equipment were a further source of information. All of them collect marketing information and make in house estimates of the number of procedures carried out yearly. Each distributor we approached provided their confidential estimates.

A final check was made to validate the figures by telephoning all centres one year after the information had initially been provided. The results of this inquiry were then compared with the original report and a further check made if they were appreciably different.

It is apparent that in the early years very few records were kept apart from the nursing procedure register, and these appear to be the most accurate source of data throughout. They are supported strongly by the estimates of commercial distributors. Figures from PTCA centres usually claimed higher numbers than could be supported from the procedure register

Table 1 Total number of patients treated each year from 1985 to 1989

Year	New PTCA cases in UK	
	Total	No/million
1985	1640	29
1986	2780	49
1987	4150	74
1988	5750	101
1989	6800	120

particularly in early years. Information from district health authorities was sometimes extremely detailed and correlated well with other sources. However, this was frequently not the case, and many health authorities have no information on the PTCA activity within their district. More accurate figures should be available in the future after the initiative of the British Cardiovascular Intervention Society in establishing an annual survey.[16]

The PTCA figures in the present report are primarily based upon the number of cases recorded in the procedure books in each centre.

4.2 AVAILABILITY

PTCA is potentially available at all cardiothoracic centres where surgical standby can be provided and is carried out in a few additional centres. The need for operator training, redistribution of catheter room schedules, and inappropriate funding prevented the procedure being introduced in some areas until recently. In 1985 angioplasty was available at 15 sites in the United Kingdom although often in small numbers and for uncomplicated lesions only. By 1987 all cardiothoracic centres were able to offer the procedure, at least to a limited extent. In 1989 PTCA was performed at 43 NHS and seven private hospitals in the United Kingdom. Table 1 shows the total numbers of patients treated each year by PTCA over this period.

4.3 REGIONAL DISTRIBUTION

The availability of PTCA is unevenly distributed across the country with over half the procedures being carried out in the London area. Table 2 shows the increase in activity in individual regions.

Table 2 Increase in activity in individual regions (1985–7)

Regional Health Authority	New cases/million		
	1985	1986	1987
East Anglia	3	3	12
Mersey	3	12	35
North East Thames	90	164	177
Northern	9	32	50
Northern Ireland	86	95	152
North Western	26	53	82
North West Thames	30	43	61
Oxford	9	9	28
South East Thames	88	140	189
South Western	8	8	4
South West Thames	9	48	58
Scotland	8	40	70
Trent	33	40	48
Wales	13	13	30
Wessex	7	13	34
West Midlands	11	18	37
Yorkshire	12	35	71

Table 3 Comparison with other countries

Country	PTCA/million			
	1985	1986	1987	1988
Australia	84	128	164	188
Austria	67	90	134	180
Belgium	111	173	264	390
France	125	142	178	272
Germany	77	139	189	265
Netherlands	187	243	324	389
Spain	20	27	37	48
Switzerland	112	123	151	205
United Kingdom	29	52	74	120
USA	452	668	742	1004

5 Comparison with other countries

Revascularisation by PTCA is increasing rapidly in all developed countries. Reports from various national bodies, publications, and local surveys are combined in table 3.

In the United Kingdom the availability of PTCA has increased fourfold since 1985. In 1988 approximately 100 procedures per million population were performed. This is still appreciably less than half the level in France, Germany, or Switzerland and is well below one third of the level in the Benelux countries. In the United States ten times as many patients per million population were treated by angioplasty as in the United Kingdom.

An investigation of PTCA availability in Europe was carried out by Van den Brand with surveys in 1986 and 1988. The number of procedures was shown to be related to the number of catheterisation laboratories in each country but not to the number of cardiologists, to the overall incidence of ischaemic heart disease, or to the gross domestic product per head.

6 Relation between PTCA and CABG

6.1 RATIO OF REVASCULARISATION PROCEDURES

In the United States the number of patients revascularised by PTCA and by CABG became approximately equal during 1988. During 1989 the numbers treated by PTCA (290 000) exceeded those having surgical bypass (250 000). This crossover point has not been reached in most other countries, but the trend is similar. Although the percentage of patients revascularised by PTCA approaches that of the United States the total procedures per million are far less. In the United Kingdom revascularisation is carried out at about one quarter the rate per million population compared with the United States, and at about half the rate per million in West Germany. Table 4

Table 4 Revascularisation performed by PTCA (1988/89)

Country	% of total
France	50
USA	50
West Germany	44
Holland	40
Switzerland	40
Spain	40
United Kingdom	30
Australia	25

shows the percentage of revascularisation procedures by PTCA in other countries.

It must be remembered that surgical procedures were almost entirely multivessel, while many of the PTCA dilatations were for single vessel disease. Multivessel PTCA is increasing rapidly and the preponderance of single vessel disease in angioplasty series is largely historical. Most high volume PTCA centres in Europe and America now carry out multivessel dilatation in most patients.

6.2 SURGICAL STANDBY

It is general practice for PTCA to be performed only when the patient can be transferred rapidly to theatre for bypass grafting in the event of abrupt closure of the artery. Some years ago urgent surgery was required after approximately 6% of procedures but the incidence has fallen to less than 2%. The original aim of providing a surgeon, anaesthetist, nursing staff, and pump technician standing by with an empty theatre during every angioplasty would be a great waste of resources, and experience no longer supports this concept.

Present policy in most centres, both abroad and in the United Kingdom, is that the patient's condition is stabilised as far as possible in the catheter room and the patient is transferred when necessary on a semi-urgent basis. This requires the surgical team to be available but not unoccupied.

In most United Kingdom centres the operating theatre and the catheterisation laboratories are not immediately adjacent and there is a considerable interval between the catheter room decision that surgery is necessary and the patient going on bypass. Our information indicates that in the United Kingdom this is usually between 45 minutes and three hours. Rather surprisingly, similar figures are reported from other countries including large centres in the United States. This interval is too long to prevent muscle damage in the event of total myocardial ischaemia from vessel occlusion but the presence of collateral circulation frequently allows surgical revascularisation with no significant damage. Acute supportive measures include distal perfusion through special catheters, re-opening of thrombosed sites, and "tacking back" of dissected flaps.

Other methods such as coronary sinus retroperfusion or intra-aortic balloon pumping are under investigation but not yet established as appropriate for this indication, because little reperfusion of the ischaemic heart is achieved.

As expected, overall results in patients in whom urgent grafting has followed complicated PTCA are less satisfactory than in purely elective procedures,[17] though the differences are not great.

6.3 ABSENCE OF SURGICAL BACKUP FOR PTCA

In many countries PTCA is carried out in patients judged to be low risk without surgical backup being available on site. Such arrangements usually involve transfer of the patient by ambulance to the surgical centre in the event of a complication and this has been shown in some instances to be successful. An average time to reperfusion of 151 minutes after occlusion was achieved in Melbourne, where the nearest surgical backup was 2 km away.[18] Reports from Dublin (B Maurer, 1990, personal communication) and Belfast[19] show identical results after PTCA complications in hospitals without surgery on site compared to those with surgery. The major delays occurred in organising bypass, not in transfer of the patient from the catheter room to the operating theatre. A possible parallel exists with the early days of coronary angiography in the United Kingdom. In 1973 the Cardiology Committee of the Royal College of Physicians considered the risks of angiography, and an editorial published in the *British Heart Journal* in 1975 included the recommendation that surgical standby should always be immediately available.[20] This proved too onerous a restriction and was largely ignored in the United Kingdom, as in all other countries. Coronary arteriography has become widely available to the United Kingdom population through hospitals without cardiac surgery. The risks of this philosophy have recently been re-emphasised in a report from St George's Hospital.[21] It is universally appreciated that these risks exist, but they are held to be so small that patients should not be denied the benefits of the procedure, even without surgical cover. It is our perception that similar development is now occurring in the field of PTCA. As an example we note that over 50% of PTCA procedures carried out in West Germany during 1988 were in hospitals without surgery on site (P Lichlen, personal communication).

The view taken by both the Joint United States/European Task Force on Coronary Angioplasty and the American College of Cardiology/American Heart Association Task Force Report on PTCA is that immediate surgical backup should always be available on site.[22 23] This position has not been universally endorsed, either in the United States or in Europe, and appears untenable in the light of present practice. If transfer to another site can be achieved fast enough for surgery to start with no more delay than on the primary site we regard this as a satisfactory alternative.

6.4 EFFICACY OF SURGICAL BACKUP

The results of urgent surgery after a complication during PTCA vary widely. Patients who can be transferred in a stable haemodynamic condition can be expected to have an excellent outcome, often with no evidence of muscle damage. On the other hand, patients in shock, possibly being maintained with external chest compression from the catheter room to the operating theatre, have a very bad prognosis. We have been unable to find convincing evidence that surgical attempts at immediate revascularisation influence the prognosis. Most published reports are descriptive, not analytical, and there are examples of patients in shock making complete recovery while others suffer significant infarction despite early grafting of a single vessel. It is extremely unlikely that any randomised trial could now be carried out.

6.5 RECOMMENDATIONS FOR SURGICAL STANDBY

It is our view that in carefully selected patients it is ethical to attempt PTCA in the absence of immediate surgical standby. This is in effect the present situation in many hospitals where logistic, staffing, or administrative problems delay the establishment of cardiac bypass. We recommend that this course is followed only when a fully trained PTCA operator has assessed the patient as low risk, and the patient belongs to one of the three following subgroups:

(i) *Previous cardiac surgery*—The presence of adhesions and distorted anatomy make surgical access to the heart slow. Previous grafts, including the internal mammary artery, may be adherent to the back of the sternum with resulting disruption of the graft if hasty access is attempted. It is impossible to offer such patients immediate surgical revascularisation although elective procedures are still available.

(ii) *Patients with extremely bad left ventricular function* may face an overwhelming surgical risk.

(iii) *Patients with concomitant illness* such as renal failure or obstructive airways disease which makes the risk of even elective surgery very high.

We do not think these patients should be denied surgical standby but they should be aware that the risks of operation after a PTCA complication will be higher than normal.

6.6 CROSSOVER PTCA TO CABG

There are several reasons why patients initially treated with PTCA may subsequently be referred for CABG. The most obvious group is where PTCA has failed. Another group is where restenosis has occurred one or more times and further PTCA is judged inappropriate by the physician or the patient. There is also a large group of patients with multivessel disease where full revascularisation is not achieved by PTCA and only the "culprit" vessel can be dilated. Published results on this procedure sometimes indicate that excellent relief from symptoms, without increased morbidity or mortality, can be achieved for several years.[24] This approach offers the possibility of postponing a major operation. Repeated PTCA may be appropriate even when symptoms deteriorate: so CABG can be avoided altogether even though total revascularisation is never achieved.

Progression of native disease will produce new lesions in many of the patients treated with PTCA and some of these will be appropriately treated with bypass grafting instead of further PTCA. Present trends indicate that the crossover rate of PTCA to CABG is approximately 20% over a five year period from the first intervention. Because coronary artery disease is a progressive disorder, often spanning many years, progressive treatments will often be needed. In many cases angioplasty is an initial revascularisation procedure that delays the need for CABG.

6.7 CROSSOVER CABG TO PTCA

Some patients undergoing bypass surgery will have inadequate revascularisation, while in others angina will develop again because of graft occlusion or progression of native disease. In addition, stenoses can develop in saphenous vein grafts, either in the area of the anastomosis or in the grafted artery distal to the insertion. Recurrence of symptoms is often caused by a single new lesion in a patient with multiple grafts. Repeat surgery can frequently be avoided in such patients by an angioplasty, either of the coronary artery or of the graft.

The implications for future planning in the United Kingdom are that increased PTCA facilities will be required to deal with the rising number of patients whose symptoms are returning after bypass graft operations, while surgical facilities will also be needed as future PTCA patients crossover to surgery.

6 8 IMPACT OF PTCA ON SURGICAL WAITING LISTS

Because many patients undergoing revascularisation are being treated by PTCA the number of bypass graft operations might be expected to fall, but experience has shown that this is not so—even in the United States. The Cleveland Clinic experience cites as a major factor the inability to obtain complete revascularisation in patients with chronic occlusions. Until recently most PTCA patients had single vessel disease while surgical patients almost invariably required multiple grafts.[25] The removal of single vessel disease from surgical referrals makes little impact on waiting lists. The prevalence of multivessel disease is such that surgical facilities in most countries are saturated and all cardiac surgical centres in the United Kingdom have a large pool of untreated patients on long waiting lists. Similar situations exist in all other European countries.

The increasing ability of interventionists to treat multivessel disease by angioplasty cannot be expected to alter the CABG situation in the United Kingdom for many years because trained operators and PTCA facilities are themselves very limited.

Resource planning in the United Kingdom cannot proceed on the basis that the need for CABG will be reduced by angioplasty. Although this point could theoretically be reached it has not been achieved even in the United States where PTCA and CABG are both being performed at a level of approximately 1000 cases per million population per year, far in excess of the figures in the United Kingdom.

7 Financial aspects

7.1 COST OF PTCA

The initial costs of the procedure are determined very largely by the number of balloons used, because these cost approximately £500–£600 each and cannot be used for another patient. Additional less important factors are whether the arm or leg approach is used, whether both left and right coronary arteries need to be cannulated, and which manufacturer's equipment has been chosen. It is often necessary for very tight stenoses to be dilated first with a small balloon which is then changed for a larger size to allow full opening of the lesion. In the United Kingdom the average number of balloons per case was 1·2 in 1986 and 1·4 in 1987.

Marginal costs (that is, disposables only) averaged over 100 procedures from six different centres in the United Kingdom during 1988 gave a figure of £1000 per case. This cost would be reduced if apparatus was resterilised and used again. Resterilising of apparatus intended for single use only has been practised in the United Kingdom and is fairly common in some European centres. We do not recommend that it continues in the United Kingdom despite the financial advantages. Characteristics of balloons, guiding catheters, or inflation pressure gauges may be significantly different after use and resterilisation. Furthermore, quality control of cleaning, removal of protein, and resterilisation is almost impossible to achieve under hospital conditions. Each item is designated by the manufacturer for single use only and we have been informed by hospital solicitors as well as by malpractice insurance societies that there would be no defence against a claim from a patient who suffered a complication when resterilised equipment had been used.

A hospital stay of two or three days must be added to the marginal costs. Comparison with the cost of CABG is inappropriate because we regard the procedures as complementary, not alternatives, for most patients. The economic benefit to the country is most likely to occur because after PTCA a patient can undergo full activities almost immediately and return to work without prolonged convalescence. Even though revascularisation by PTCA is cost effective for an individual patient the very large number of patients who can potentially benefit represents a large future financial commitment.

A projection for the United Kingdom, based on PTCA becoming available at only one third of figures in the United States, suggests that appropriate future planning should allow for 300 to 500 patients per million population treated yearly by coronary angioplasty within five years. This is approximately twice the total number of patients revascularised in the United Kingdom by surgery and angioplasty combined at present.

Such planning will need to identify a realistic growth rate, related to financial resources and also to availability of trained staff. Any catheterisation centre expanding its PTCA service will require at least two laboratories or it will become impossible to perform sufficient diagnostic angiograms.

8 Facilities for coronary angioplasty

8.1 CATHETERISATION LABORATORIES

The minimum requirements do not differ from those necessary for a modern suite in which diagnostic cardiac catheterisation is performed. High resolution fluoroscopic and cineangiographic or digital x ray unit, the ability to display different magnifications, and to perform craniocordial views are essential. The imaging system must be capable of showing a narrow (0·010 inch) guidewire clearly in all projections and of displaying still "road map" frames simultaneously with real time screening. High resolution video or digital storages systems meeting these requirements are still rare in United Kingdom laboratories. Particular attention should be paid to radiation protection because times are likely to be considerably longer than in diagnostic investigations. A display system continually drawing the operator's attention to the elapsed fluoroscopy time is highly desirable. It is mandatory for operators to wear protective glasses and thyroid shields in addition to the usual lead apron.

A considerable inventory of stock is also necessary, including a selection of balloon catheters with dimensions from 2·0 to 3·5 mm, and a wide selection of guiding catheters. Several inflation/deflation devices should be available and an ample supply of guidewires. Devices for use in complications are becoming more widely available and are an additional cost.

8 2 OPERATOR TRAINING

The safety and success of coronary angioplasty depend greatly on the skill, experience, and training of the operator; the potential for disaster is very much greater than during diagnostic catheterisation. Good results can be achieved only when a continuing high number of cases are treated. It seems likely that this will be achieved in the United Kingdom for each cardiothoracic centre because the number of potential patients is so large and the number of centres relatively small. The number of operators should be restricted so that those performing the procedure have high enough volume to maintain their skills. In suggesting the following guidelines for the training of angioplasty operators the working group does not wish to be restrictive but to encourage the expansion and most effective use of opportunities.

(i) Candidates training as angioplasty operators should already be skilled in diagnostic coronary arteriography.

(ii) Attendance at formal training courses is encouraged.

(iii) The most important aspect is hands on experience which should initially be obtained by assisting an experienced operator. We suggest that 50 procedures should be performed in this way before the trainee acts as a primary operator. After these 50 cases an experienced angioplasty operator should be available nearby to advise and if necessary take over the procedure in case of difficulty.

9 Policy

We do not recommend that experience in PTCA should be a requirement for accreditation in cardiology but the importance to the NHS of training an adequate number of operators should be recognised by the granting of appropriate study leave and expenses to suitable candidates. These recommendations are in keeping with guidelines expressed by the ACC/AHA Task Force Report[22] and the International Society and Federation of Cardiology/World Health Organisation Task Force on Coronary Angioplasty[23] as well as the present practices adopted by major angioplasty centres abroad.[26]

10 Future developments

10.1 COMPARATIVE TRIALS

It is well documented that CABG improves the prognosis compared with medical treatment but it is too soon for comparable data to be available for PTCA. Future clinical practice is likely to be influenced by the results of several trials under way at the moment to compare PTCA with alternative treatments. These include the British RITA (Randomised Intervention Treatment of Angina) trial, the German GABI (German Angioplasty Bypass Surgery Investigation) trial, the European CABRI (Coronary Angioplasty Bypass Randomization Investigation) trial, the American BARI (Bypass Angioplasty Randomization Investigation) trial, and the Emory University EAST (Emory Angioplasty versus Surgery Trial). In addition, a trial comparing PTCA with medical treatment ((ACME) Angioplasty Compared to Medicine trial) is under way at Providence, USA. By the end of 1989 approximately 2500 patients had been entered into these randomised trials, the first of which began in 1986. Because most protocols require a follow up of five years clinical decisions cannot be postponed until results are available.

10.2 TECHNICAL ADVANCES

Equipment used for angioplasty is improving very rapidly and new techniques are under active investigation. These include transluminal atherectomy, lasers, intracoronary stents, high speed and low speed rotation devices, ultrasonic fragmentation, hot-tip catheters of various types, and spark erosion catheters. All must be regarded as still experimental. Both the results of the trials and the development of experimental technical devices emphasise the need for this report to be revised within a few years.

The very rapid development of angioplasty during its first 10 years leads inevitably to the conclusion that the potential for treating more complicated disease will greatly increase and the number of patients who can benefit will be very much larger.

11 Comments and conclusions

The increase in coronary angioplasty treatment in the United Kingdom has been slower than in most European countries, and this method of treatment is available to a smaller proportion of the population than elsewhere. Major limiting factors are the pressure for diagnostic catheterisation, which competes for time with angioplasty procedures in the catheter room, the relatively few trained operators, and the increasing cost of large numbers of procedures. There is no justification for the view that increase in angioplasty will reduce the need for cardiac surgery in the United Kingdom in the foreseeable future. Future planning should consider provision of additional catheter laboratories to accommodate the need for PTCA and take particular note of the rate of growth which is likely to follow the same pattern as elsewhere in Europe. Even a modest regular increase in availabiity of angioplasty in the United Kingdom over the next few years, without attempting to match levels in the United States, requires provision for approximately 25 000 patients yearly. This will involve the training of new operators, which must be started now if they are to be ready to deal with the increased workload in a few years' time.

We thank the catheter room sisters and colleagues in centres throughout the country who have freely provided information.

1 Gruntzig AR. Transluminal dilatation of coronary-artery stenosis *Lancet* 1978,i:263
2 Reeder GS Angioplasty and the cost of myocardial revascularization has its promise been fulfilled? *Int J Cardiol* 1987,15.287–92.
3 Little T, Mukherjee D, Lee K, Milner MR, Pichard A, Lindsay J Jr Coronary angioplasty in octogenarians [abstract]. *J Am Coll Cardiol* 1990;15 (suppl).35A
4 Meier B. Kissing balloon coronary angioplasty *Am J Cardiol* 1984,54·918–20.
5 O'Keefe JH Jr, Holmes DR Jr, Reeder GS, Bresnahan DR A new approach for dilation of bifurcation stenoses· the dual probe technique *Mayo Clin Proc* 1989,64 277–81
6 DiSciasio G, Vetrovec GW, Cowley MJ, Wolfgang TC Early and late outcome of percutaneous transluminal coronary angioplasty for subacute and chronic total coronary occlusion. *Am Heart J* 1986;111:833–9.
7 De Feyter PJ, Suryapranata H, Serruys PW, Beatt K, von Domburg R, van den Brand M, *et al.* Coronary angioplasty for unstable angina immediate and late results in 200 consecutive patients with identification of risk factors for unfavorable early and late outcome *J Am Coll Cardiol* 1988,12:324–33
8 O'Keefe JH Jr, Rutherford BD, McConahay DR, Ligon RW, Johnson WL Jr, Giorgi LV, *et al* Early and late results of coronary angioplasty without antecedent thrombolytic therapy for acute myocardial infarction. *Am J Cardiol* 1989;64 1221–30
9 Simoons ML, Betriu A, Col J, von Essen R, Lubsen J, Michel PL, *et al* Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet* 1988;i 197–203
10 Platko WP, Hollman J, Whitlow PL, Franco I. Percutaneous transluminal angioplasty of saphenous vein graft stenosis: long-term follow-up. *J Am Coll Cardiol* 1989;14 1645–50.
11 Lee TC, Hartzler GO, Rutherford BD, McConahay DR, Johnson WL Jr, Giorgi LV, *et al.* Does previous bypass surgery increase risks in elective percutaneous coronary angioplasty? [abstract] *J Am Coll Cardiol* 1990,15 (suppl) 13A
12 Sowton E. Coronary angioplasty as a salvage procedure. In. Vecht RJ, ed. *Angioplasty.* London Pitman Publishing, 1984·92–6
13 Joly P, Bonan R, Palisaitis D, Cequier A, Crepeau J, Cote G, *et al* Treatment of recurrent restenosis with repeat percutaneous transluminal coronary angioplasty *Am J Cardiol* 1988,61.906–8.
14 McBride W, Lange RA, Hillis LD. Restenosis after successful coronary angioplasty. *N Engl J Med* 1988; 318:26 1734–7.
15 Talley JD, Hurst JW, King SB III, Douglas JS Jr, Roubin GS, Gruentzig AR, *et al.* Clinical outcome 5 years after attempted percutaneous transluminal coronary angioplasty in 427 patients. *Circulation* 1988;77·820–9.
16 Hubner PJB. Audit. an independent report Cardiac interventional procedures in the United Kingdom during 1988. *Br Heart J* 1990;64:36–7
17 Naunheim KS, Fiore AC, Fagan DC, McBride LR, Barner HB, Pennington DG, *et al.* Emergency coronary artery bypass grafting for failed angioplasty· risk factors and outcome *Ann Thorac Surg* 1989;47 816–23
18 Saltups A, Goldstein J, Cooper E. PTCA with off-site surgical standby [abstract]. Proceedings of the Thirty-sixth Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand; 8–11 May 1988 35/9.
19 Richardson SG, Morton P, Murtagh JG, O'Keeffe DB, Murphy P, Scott ME. Management of acute coronary occlusion during percutaneous transluminal coronary angioplasty; experience of complications in a hospital without on site facilities for cardiac surgery *BMJ* 1990;300:355–8.
20 Emanuel R. Coronary arteriography. *Br Heart J* 1975; 37.229–30.
21 Stewart JT, Gray HH, Ward DE, Pumphrey CW, Redwood DR, Parker DJ, *et al.* Major complications of coronary arteriography the place of cardiac surgery *Br Heart J* 1990;63:74–7.
22 Guidelines for percutaneous transluminal coronary angioplasty. ACC/AHA Task Force Report 1988 *J Am Coll Cardiol* 1988;12·529–45.
23 Report of the Joint International Society and Federation of Cardiology/World Health Organization Task Force on Coronary Angioplasty. *Eur Heart J* 1988,9 1034–45.
24 Reeder GJ, Vliestra RE, Bailey KB, Holmes DR Jr. Revascularization by percutaneous transluminal coronary angioplasty: how much is enough? *Int J Cardiol* 1988,21:99–103.
25 Hollman J. The limited impact of percutaneous coronary artery angioplasty on bypass surgery. *Int J Cardiol* 1988,20.193–200.
26 Meier B. Gaining, maintaining, and surveying competence in the interventional cardiology laboratory. *Int J Cardiol* 1990;29:9–14.

BRITISH CARDIAC SOCIETY NEWSLETTER

The newsletter this month is principally about meetings planned by the British Cardiac Society. To encourage members to support the European Society of Cardiology we decided that we should have only one major meeting a year We believe this was the correct decision but the reduction in our own activities left a void that we have failed so far to fill. We have a suggestion that is relatively minor but it may answer a need. We will try a cautious pilot scheme, and develop the idea if it proves popular. In the meantime we welcome your views.

Our suggestion is for small meetings at the British Cardiac Society for approximately 20 members, selected on a first apply first accepted principle. The meetings will cover topics that should be of general interest to cardiologists yet are outside the expertise of most of us—and without some help likely to remain so. They will be led by an expert, but will be interactive with the lively audience participation that should easily be generated within a small group. The first meeting will be at 10 am on Tuesday 18 February 1992 on the topic of molecular biology with particular reference to our specialty. The second, which is planned for 10 am on 9 June, is entitled "New Concepts in the Pathophysiology of Atheroma". Details will be announced in due course. The meetings will be quite different from the excellent workshops held by the British Heart Foundation that are attended by experts with a common interest. Our meetings will assume little prior knowledge and will be designed to offer an introduction to the subject (and whet the appetite for more). The late start should enable members remote from London to attend. Those who live and work a long way from the capital are at a disadvantage in terms of easy access for many meetings, to say nothing of expense. Would it be fair to subsidise travel for those who have far to come? This has not been agreed but if members favoured the idea we could consider it No charge would be made for the meetings of course. If you wish to attend either of the first two meetings you may feel you should apply at once—we would be delighted if there were a rush . . . If the idea should prove to be popular the seminars could become regular events, one in each month that had no major American or European meeting—perhaps eight a year. Do please give us your views on all these various points

We are planning two special meetings this year. The first, by invitation only, is on 29 November and is for representatives of our affiliated groups: BCIS (interventionalists), BPEG (electrophysiologists), BNCG (nuclear cardiologists), BSE (echocardiographers), and BPCA (paediatric cardiologists). We have never defined what we mean by an affiliated group We wish to know what the groups wish affiliation to mean and what they want the society to do for them We need to determine how far the society should seek to have an influence on matters of common interest—for example the reports that are issued from time to time by the groups. The Association of British Cardiac Nurses also seeks affiliation but before this matter is discussed further we believe it is wise to consider further the meaning of affiliation.

The second meeting is planned for 4 December. This will be for a restricted number of members, perhaps 50 in all, again on a first apply first accepted principle. It will address matters relating to the development of the internal market in the National Health Service. John Parker has drawn attention to the need for the meeting, and has undertaken to supervise the arrangements. Cardiology and cardiac surgery face many special problems as average specialty cost contracts evolve to individual procedure and diagnostic costs. These difficulties are complicated by the extensive cross referral between districts in our specialties. Other issues to be considered will include the identification and funding of research activity in both district general hospitals and regional centres. It is hoped that the participants will include representatives from the Department of Health, the National Health Service Management Executive, and a health economist, as well as representatives from the provider and purchaser side, including a regional director of public health. Please let us know if you wish to attend.

Finally news of a meeting of the British Nuclear Cardiology Group, to be held in association with the British Institute of Radiology. The title is "Ischaemic Heart Disease: Limitations of Non-invasive Assessment", the venue is the Bearstead Lecture Theatre at The Royal London Hospital (10.30 am to 4.30 pm on Friday 22 November). Stuart Cobbe will present the general possibilities for assessment and risk stratification. Other speakers will discuss the advantages and limitations of a wide range of specific techniques from the familiar—electrocardiography, echocardiography, perfusion imaging, and blood pool imaging—to the more novel such as nuclear magnetic resonance and fast computed tomography. Debate between the experts and the audience will be encouraged—indeed stimulated—by Martin Rothman. The registration fee is £10 (£5 for technicians). More information on what should prove to be a lively occasion can be obtained from Ann Tweddel at Glasgow Royal Infirmary (041 552 3535 ext 5362).

Several important reports are due to appear in the next few months. These include the Sixth Biennial Survey of Staffing in Cardiology, which will appear in the next issue of the journal. This will highlight potential problems in staffing for the coming years: as data are available problems should be avoided, but first they have to be understood and accepted. We hope they will be. Accurate and recent data are so important to us in our frequent debates over staffing and training that we are now to conduct surveys annually instead of biennially. Bear with us. We need the information for the good of the specialty, our units, and of course our patients. There is also a report from BCIS to appear in the *British Heart Journal* and one from a working party on cardiological services for the elderly to appear in the Journal of the Royal College of Physicians. The BPEG recommendations for pacemaker prescription for symptomatic brachycardia appeared in the August issue of the *British Heart Journal.* The Fourth Report of a Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England on the provision of services for the diagnosis and treatment of heart disease should appear early next year

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society,
1 St Andrew's Place,
London NW1 4LB

NOTICES

1992

The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre on 26 to 29 May. The closing date for receipt of abstracts is 3 January 1992.

The **Vth World Congress of Cardiac Rehabilitation**, organised by the Scientific Council of the Section on Cardiac Rehabilitation of the International Society and Federation of Cardiology, will take place in Bordeaux on 5 to 8 July: BCS, Palais des Congrès de Bordeaux, 33300 Bordeaux-Lac, France (Fax: (+33) 56 43 17 76; Tel: (+33) 56 50 84 49).

American Heart Association

Fast-Fax

Subscription Service

1 (214) 691-2704

The American Heart Association invites you to telefax your journal order directly to us. Your personal subscription will be processed quickly and delivery will be dependable. Institutional rates are available on request.

Journal Subscription Fax-Form

Please check the boxes on the right for the journals you wish to receive.)verseas issues are sent by air-expedited service. US copies are sent by the United States Postal Service.

This form is designed to be telefaxed. If you prefer to mail your order, simply complete the fax-form and mail it to:

American Heart Association
Scientific Publishing
7320 Greenville Avenue
Dallas, TX 75231-4599
USA

or

Telephone your order by calling:
1 (214) 706-1310

Charge your subscription to a credit card or send a check directly to the AHA. Advance payment is required.

* For rate information in Japan, contact nkodo Co. Ltd., 42-6 Hongo 3-chome, Bunkyo-ku Tokyo–113 Japan
Fax 03-811-5031

'15C

Journals	No. of Issues	International Rate *	US Rate
☐ ***Arteriosclerosis and Thrombosis***	6	US $118	$98
☐ ***Circulation***	12	US $152	$92
☐ ***Circulation Research***	12	US $194	$132
☐ ***Hypertension***	12	US $130	$96
☐ ***Stroke***	12	US $134	$92
☐ ***Cardiovascular Nursing***	6	US $15	$6
☐ ***Currents in Emergency Cardiac Care***	4	US $8	$8

Amount $ ____________

Name ____________

Address ____________

____

____

City ____________

Country ____________ State ____________

Telephone ____________ Fax ____________

Start my subscription with the ____________ issue.

My specialty is ____________

☐ I would like to receive a confirmation of my fax order.

☐ Check enclosed — Make checks payable to the American Heart Association in US dollars drawn on a US bank

☐ Visa VISA ☐ MasterCard MasterCard

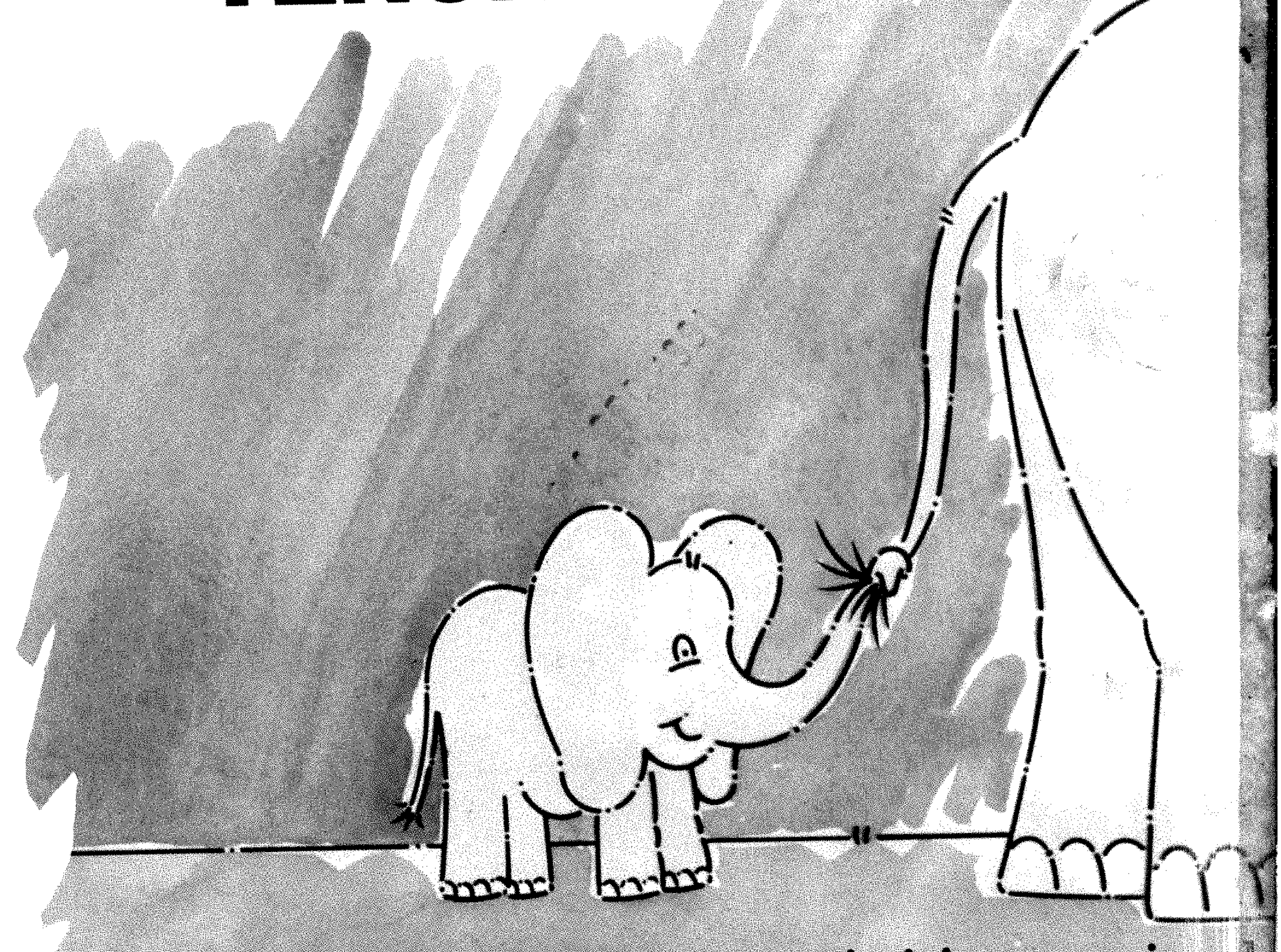
Card number ____________ Expiration date ____________

Signature ____________

This offer expires December 31, 1991

DON'T FORGET!

TENORMIN 25



When a lower dose of 'Tenormin' is required
– in renal impairment

Tenormin 25
atenolol 25mg

Prescribing notes for Tenormin atenolol 100mg Tenormin LS atenolol 50mg Tenormin 25 atenolol 25mg

Consult data sheet before prescribing.

USE: Hypertension, angina prophylaxis

PRESENTATION: Tablets for oral administration containing atenolol 100mg ('Tenormin'), 50mg ('Tenormin' LS) or 25mg ('Tenormin' 25).

DOSAGE AND ADMINISTRATION: Hypertension: 'Tenormin' – one daily (some patients may respond adequately to 'Tenormin' low strength (LS)). 'Tenormin' LS – one daily; 'Tenormin' 25 – see renal failure.

Angina Prophylaxis: 'Tenormin' – one daily. 'Tenormin' LS – two daily in a single or divided dose.

Children: 'Tenormin', 'Tenormin' LS and 'Tenormin' 25 are not recommended for use in children.

Elderly Patients: Dosage requirements may be lower in elderly patients.

Renal Failure: For patients with a creatinine clearance of 15-35ml/min/1.73m^2 the oral dose should be 50mg daily. Patients with a creatinine clearance of <15ml/min/1.73m^2 should be given one 'Tenormin' 25 daily or one 'Tenormin' LS on alternate days.

CONTRAINDICATIONS: 2nd or 3rd degree heart block, cardiogenic shock.

PRECAUTIONS: Poor cardiac reserve – avoid in overt heart failure. Bradycardia, renal failure (see above), anaesthesia, pregnancy. Caution in patients with reversible obstructive airways disease – do no unless there are compelling clinical reasons to do so. Atenolol modifies the tachycardia of hypogly Co-administration with verapamil or Class I antidysrhythmic agents. Withdrawal of clonidine. With beta-blocking drugs should be gradual in patients with ischaemic heart disease.

SIDE EFFECTS: Coldness of extremities, bradycardia and muscular fatigue may occur. Sleep dis rarely seen. Skin rashes and dry eyes have been reported with beta-blockers – consider discontin they occur.

PRODUCT LICENCE NUMBERS AND BASIC NHS COSTS: 'Tenormin' (29/0022), 28 tab £6.98. 'Tenormin' LS (29/0086), 28 tablets (OP) £5.49. 'Tenormin' 25 (29/0218), 28 tablets (OP

'Tenormin', 'Tenormin' LS and 'Tenormin' 25 are trademarks.

Further information is available from
Stuart Pharmaceuticals, King's Court,
Water Lane, Wilmslow, Cheshire SK9 5AZ

STUAR
May '91/2